CENTRAL NERVOUS SYSTEM PENETRATION OF COMBINATION ANTIRETROVIRAL THERAPY: THE CEREBROSPINAL FLUID (CSF) RISK SCORE, THE BURDEN OF CSF VIRAL ESCAPE, AND DEPRESSION IN PERSONS WITH HIV

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ABSTRACT

BACKGROUND: Detectable cerebrospinal (CSF) HIV ribonucleic acid (RNA) is associated with central nervous system (CNS) complications including neurocognitive impairment and depression. Major depressive disorder (MDD) is the most common neuropsychiatric complication in persons with HIV, and is associated with poor virologic outcomes and faster HIV progression.

METHODS: This dissertation utilized data from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, a six-center, US-based prospective, cohort study. First, we developed a prediction model to estimate the risk of detectable CSF HIV RNA (threshold >50 copies/ml). Second, we evaluated the association between detectable CSF HIV RNA and depression. Third, we determined the prevalence and incidence of CSF viral escape, defined as detectable CSF HIV RNA in the presence of undetectable plasma HIV RNA. Fourth, we evaluated the association between the CSF HIV Risk Score and new-onset CSF viral escape and suggest thresholds for clinical use.

RESULTS: Study 1: Plasma HIV RNA, CNS Penetration Effectiveness (CPE), duration of cART, adherence, race and depression status were retained as predictors of detectable CSF HIV RNA. The CSF HIV Risk Score ranges from 0 to 42 points, displaying good calibration, Hosmer-Lemeshow p-value=0.85, and discrimination, c-statistic=0.84.

Study 2: Detectable CSF HIV RNA (threshold ≥50 copies/ml) at any visit was associated with a 4.7-fold increase in new-onset depression; adjusted hazard ratio (HR)=4.76, 95% Confidence Interval [CI]: 1.58, 14.3; P=0.006).
Study 3: The overall prevalence of CSF viral escape at baseline was 17.6%. The incidence of CSF viral escape was higher in persons with MDD; HR=3.01; 95%CI: 1.03, 8.78, P=0.043).

Study 4: The CSF HIV Risk score at cut-point ≥16 was associated with 90.1% sensitivity (95%CI: 81.8, 96.3), and 99.1% specificity (95%CI: 97.8, 99.7), for detecting CSF viral escape. The risk of new-onset CSF viral escape in persons with CSF Risk Scores ≥16 was over 7-fold higher compared to risks scores <16, adjusted HR=7.97 (95%CI: 3.81, 16.5), P<0.001.

CONCLUSION: Ongoing CSF viral replication may occur more frequently than previously estimated. The CSF HIV Risk Score may be used to assess CSF viral escape. Our findings may translate into improved HIV care and reduction in the neuropsychiatric complications of HIV.
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“And He is before all things, and by Him all things consist.” -Colossians 1:17, KJV

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Dedication

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CHAPTER 1

INTRODUCTION
OVERVIEW

Depression is the most common psychiatric disorder associated with HIV/AIDS with a lifetime prevalence of 22-45% (Krishnan et al., 2002; Rabkin, 2008). Neurocognitive disorders associated with HIV (HAND) are common clinical disorders among persons infected with HIV with prevalence ranging between 5-60% despite HAART treatment (Joska, Gouse, Paul, Stein, & Flisher, 2010). The introduction of combination antiretroviral therapy (cART) has improved survival and reduced opportunistic infections, however high rates of cognitive impairment and depression continue to occur (Strazielle & Ghersi-Egea, 2005).

Depression has been shown to increase the risk of acquiring and transmitting HIV, decrease adherence to treatment, and increase mortality (Alvy et al., 2011; DiMatteo, Lepper, & Croghan, 2000; Lima et al., 2007; Whetten et al., 2006). Progression of HIV increases the risk for developing depression (Lyketsos et al., 1996). Prevention of depression and understanding the mechanism of HIV-induced depression is therefore a priority.

STUDY RATIONALE

Several studies in medically related depressive disorders have suggested a role for inflammatory cytokines as provocateurs of depression (Anisman, Merali, & Hayley, 2008; Cook et al., 2004; Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008; Raison, Capuron, & Miller, 2006; Raison et al., 2009; Raison et al., 2010). Inadequate control of CNS viral replication may increase CNS inflammation and CNS injury. CNS
inflammation associated with low-level CNS viral replication may play a role in the development of depression.

It is hypothesized that a higher concentration of anti-HIV medication in the central nervous system (CNS) is associated with beneficial neurological response. Persistent CNS virus despite suppression of plasma viral replication, known as CSF viral escape, has been reported (Canestri et al., 2010; Eden et al., 2010; Peluso et al., 2012). CSF viral escape is associated with HAND, depression and neurological deficits in HIV. This suggests that the CNS may be a viral sanctuary from which depression and neurocognitive impairment may result, even in persons treated with cART.

In the United States, there are no official guidelines for CSF testing in managing HIV disease. The concept of CNS penetration effectiveness (CPE) of cART improves estimation of concentration of anti-HIV medication that enters the CNS (S. Letendre et al., 2008; Letendre, Ellis, Ances, & McCutchan, 2010). CPE scores are based on the extent of CNS penetration suggested by chemical properties of the drug, CSF drug concentration based on human and animal studies, and demonstrated effectiveness in reducing CSF viral load or improving cognition in clinical studies. It has been demonstrated that detectable levels of CNS virus correlates with dementia, and that better CPE scores correlate with better control of viral replication (Garvey et al., 2011). However it has not yet been shown that better CPE scores correlate with decreased depression in persons with HIV.

This dissertation, which is composed of four studies, examines the concept of CNS penetration of cART and its association with depression and CSF viral escape.
The Introductory Chapter provides an overview of the thesis, the study rationale, and specific aims. Chapter 2 is a review of pertinent scientific literature related to depression in HIV, drug transport into the CNS, and CNS penetration of cART. Chapter 3 describes the first study, which evaluates the performance of the CPE score in predicting detectable CSF HIV RNA at a threshold of 50 copies/ml. This chapter also describes the development of a new risk score, the CSF HIV Risk Score, to predict detectable CSF HIV RNA. Chapter 4 provides a description of the second study that evaluates the association between detectable CSF HIV RNA and new-onset depression (mild-to-moderate depressive symptoms), in persons with HIV who were without depression at study entry. The third study, Chapter 5, describes the burden of CSF viral escape and provides the first representative estimates of the prevalence and incidence of CSF viral escape. Chapter 5 also describes the risk of CSF viral escape in persons with comorbid major depressive disorder. In Chapter 6, we describe a fourth study that assesses the association between the CSF HIV Risk score and CSF viral escape, and provides test properties of the CSF HIV Risk Score that can be applied in clinical practice. The final Chapter 7, presents a summary of this dissertation, it’s public health significance and directions for future research.

This Dissertation utilizes data from the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) prospective cohort study. We proposed the following study aims:
SPECIFIC AIMS

**Aim 1:** To develop a risk score to estimate the probability of detecting CSF HIV RNA (threshold 50 copies/ml) in persons with HIV. We will evaluate the performance of the CPE score in predicting detectable CSF HIV RNA.

**Hypothesis:** A risk score for detectable CSF HIV RNA will be beneficial in predicting persons who may benefit most from routine CSF testing.

**Aim 2:** To ascertain the relationship between detectable CSF HIV RNA and depression in HIV. We will evaluate whether persons who have detectable CSF HIV RNA (threshold 50 copies/ml) are at a higher risk of depression.

**Hypothesis:** Depression in HIV is caused in part by CNS inflammation due to HIV virus activity. Persistent CSF HIV RNA is associated with increased risk of depression.

**Aim 3:** To determine if depression in HIV is associated with CSF virologic failure independent of CNS penetration effectiveness. We will examine if persons with depression have increased risk for CSF virologic failure, defined as detectable CSF HIV RNA in the presence of clinically undetectable plasma HIV RNA levels, or CSF HIV RNA levels ≥1 log greater than the plasma HIV RNA level.

**Hypothesis:** Depression is associated with higher rates of CSF HIV viral production.

**Aim 4:** To evaluate the association between the CSF HIV Risk score and new-onset CSF viral escape. We will determine if persons with higher CSF HIV Risk
Scores are at increased risk of CSF viral escape over time. We will provide test performance characteristics and suggest thresholds of the CSF HIV Risk Score for use in clinical practice.

**Hypothesis:** The CSF HIV Risk Score predicts new-onset CSF viral escape.

The use of the concept of CNS penetration of cART is innovative and will elucidate the role of cART regimens in improving depression. This will help enhance our understanding of management and therapeutic choices for patients with HIV/AIDS. Our findings may be helpful in planning future trials that could provide information to guide the development of HIV treatments that have an additional effect of improving mood.
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CHAPTER 2

LITERATURE REVIEW
The Burden of Human Immunodeficiency Virus Infections

Worldwide it is estimated that 33.3 million persons were living with Human Immunodeficiency Virus (HIV) infections in 2009 (UNAIDS, 2011). The UNAIDS HIV Report estimates 2.6 million (2.3 – 2.8 million) new HIV infections and 1.8 million (1.6 – 2.3 million) HIV related deaths in 2009 worldwide (UNAIDS, 2011). In the United States, the Centers for Disease Control and Prevention (CDC) estimates that 1.1 million persons were living with HIV at the end of 2009 (CDC, 2011). In 2010, an estimated 45,700 new HIV infections were reported in the United States (CDC, 2012).

The introduction of combination antiretroviral therapy (cART) has improved survival and reduced opportunistic infections (Brodt et al., 1997; Tan, Smith, von Geldern, Mateen, & McArthur, 2012). Depression and neurocognitive impairment continue to be consistently associated with HIV even in the era of cART (McArthur et al., 2004; McArthur, Steiner, Sacktor, & Nath, 2010; Sherr, Clucas, Harding, Sibley, & Catalan, 2011; Tan & McArthur, 2011).

Major Depressive Disorder (MDD) is the most common psychiatric disorder associated with HIV/AIDS (Rabkin, 2008; Zanjani, Saboe, & Oslin, 2007). The lifetime prevalence of depression in the general population is estimated at between 5-17% compared to 22-45% in those living with HIV/AIDS (Kessler et al., 2005; Krishnan et al., 2002; Rabkin, 2008). Neurocognitive disorders associated with HIV (HAND) are common clinical disorders among persons with HIV. Prevalence estimates of HAND range between 5-60% (Joska, Gouse, Paul, Stein, & Flisher, 2010). Depression in HIV has been shown to be associated with incident cognitive impairment in HIV. Although the introduction of cART in 1996 has improved survival and reduced opportunistic
infections in persons infected with HIV (Strazielle & Gherzi-Egea, 2005), the burden of depression remains high (Kacanek et al., 2010). In the cART era, the prevalence of depression is unchanged, varying widely and estimated at between 15-71% (Bing et al., 2001; Judd et al., 2000; Kacanek et al., 2010; Kilbourne et al., 2001; Low-Beer et al., 2000; Rodkjaer, Laursen, Balle, & Sodemann, 2010; Sherr et al., 2011).

The various mechanisms by which HIV may cause depression or neurocognitive disorders are still being researched extensively but recent work on medically related depression in other conditions has implicated ongoing CNS inflammation and cytokines (Anisman, Merali, & Hayley, 2008; Capuron et al., 2003; Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008; D’Mello, Le, & Swain, 2009; Felger et al., 2007; A. H. Miller, Maletic, & Raison, 2009; Quan & Banks, 2007; Raison et al., 2009). The ability of anti HIV medication to reach the nervous system may be the primary modulator of depression and neurocognitive disorders in persons with HIV.

**Drug Transport into the Central Nervous System**

The main classes of antiretroviral medication include protease inhibitors (PIs), nuleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors and entry inhibitors (Qian, Morris-Natschke, & Lee, 2009). The combination of 3 or more antiretroviral medications of particular classes forms the basis of cART regimens (Gazzard et al., 2008).

Estimating the amount of drug penetration of antiretroviral drugs in the CNS is made difficult by the existence of the blood brain barrier and the blood-CSF barrier,
both of which possess various mechanisms that limit the entry of a variety of substances into the brain. Because transport mechanisms in the blood brain barrier and blood-CSF barrier differ from each other, it suggests that drug transport into the brain depends on its main route of entry. This further provides reason why drug concentration in the CSF may be different from the actual concentration in the brain. Insufficient penetration of antiretroviral drugs into the CNS may render the CNS a viral sanctuary, which may increase the risk of depression and neurocognitive disorders even in persons treated with cART.

The 2011 European AIDS Clinical Society provides guidelines for measuring CSF HIV RNA levels as a component of their clinical strategy for managing HAND (European AIDS Clinical Society, 2012). In the United States however, there are no such guidelines for managing HAND, and for that matter depression in HIV.

Central Nervous System Penetration Effectiveness of Antiretroviral Therapy

Letendre et al. recently described a concept of CNS penetration effectiveness (CPE) of cART (Letendre et al., 2008; Letendre, Ellis, Ances, & McCutchan, 2010). This method of classification assigns individual antiretroviral medications with a rank (one through four), based on CNS penetration category. Table 2-1 shows the CPE classification of frequently used antiretroviral drugs (Letendre et al., 2010). Derivation of the class of penetration is based on (i) chemical properties suggesting extent of penetration, (ii) concentration of drug in CSF based on human and animal studies or comparison of CSF concentration of drug compared with half the maximum inhibitory concentration (IC50), a measure of the extent to which the anti-HIV drug is
effective in inhibiting the virus, and (iii) demonstrated effectiveness in reducing CSF viral load or improving cognition in clinical studies. The classification of anti-HIV drugs by the CPE score is an advance in determining antiretroviral drug penetration into the CNS. The concept of CPE scores circumvents measuring CSF drug concentrations directly, but it may not accurately predict the CNS concentration of anti-HIV drugs under the operative assumption that CNS penetration increases linearly with increasing CPE scores. The CPE score may further be limited because it does not take into account interactions of drug combinations at the blood-CSF interface. Also, CPE scores may not address the potential variability of drug transport and drug penetration that may exist between the various levels of CPE scores.

**Depression in Persons with HIV/AIDS**

Depression is commonly associated with HIV infection. Among persons with HIV or Acquired Immune Deficiency Syndrome (AIDS), depression may affect the young and old equally, unlike in the general population where both the risk of current and lifetime depression increases with age (Justice et al., 2004). The prevalence of depression among persons with HIV varies widely depending on the measures used and sample size considerations.

In a recent systematic review of interventions in HIV and depression (Sherr et al., 2011), only 18 of 97 of included studies report the prevalence of depression according to a clinical diagnosis or based on a cut-point of an instrument such as the Centers for Epidemiologic Studies-Depression scale (CES-D), Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D) and Hopkins Symptom
Checklist-25. In seven of these 18 studies, which had sample sizes greater than 100 participants, the prevalence of depression ranged between 26% and 71% (Sherr et al., 2011).

In the general population, men who have sex with men (MSM) have higher rates of depression than non-MSM (Herek & Garnets, 2007). The lifetime prevalence of depression in non-intravenous drug using MSM is 32%, comparable to young men with HIV (39%), and older men with HIV (36%), but higher than older men who are not infected with HIV (20%) (Rabkin, McElhiney, & Ferrando, 2004). A meta-analysis of 10 studies investigating depression among HIV infected persons suggests a two-fold increase in risk of depression among HIV positive vs. HIV negative persons (Ciesla & Roberts, 2001). Depression among MSM has been shown to be associated with increased risk of transmission and acquisition of HIV (Alvy et al., 2011).

HIV/AIDS and depression are inter-related. Depressed individuals are more likely to contract HIV through engaging in risky behavior than non-depressed individuals. These behaviors include having sex for money or drugs, having sex when intoxicated by drugs or alcohol, having sex with intravenous drug users, and having a greater number of lifetime sexual partners (Hutton, Lyketsos, Zenilman, Thompson, & Erbelding, 2004). HIV infected persons are more likely to engage in risky behaviors that expose others to HIV (Alvy et al., 2011).

In some persons, depressive symptoms may precede the knowledge of diagnosis with HIV (Justice et al., 2004). There is also evidence to suggest that a new diagnosis of HIV can lead to new onset depression (Hutton et al., 2004). The stigma
of being HIV positive predicts depression and negative affect (Angelino, 2002; Jin et al., 2006; Simbayi et al., 2007). Persons with HIV may have emotional and psychological challenges in the face of the difficult decisions that have to be made regarding the HIV infection (Bravo, Edwards, Rollnick, & Elwyn, 2010). Some of the difficult issues that impact the mental health of persons with HIV include whether to, and to whom the diagnosis of HIV be disclosed, treatment adherence decisions, and considerations for sexual activity including desires to have a family of their own (Bravo et al., 2010).

Progression of HIV infection is associated with increased risk of depression (Lyketsos et al., 1996). Increasingly, inflammatory mechanisms have been implicated in depression. Synergistic mechanisms between major MDD and HIV may occur due to decreased cobalamin in the brain, thereby increasing the risk of MDD. The resultant effect is suppression of natural killer (NK) cells and CD8+ T cells, which may make HIV worse (Baldewicz et al., 2000). Depressive symptoms in HIV have been associated with lower NK cell activity and higher activated CD8+ T lymphocyte levels and viral load (Evans et al., 2002). Conversely, an increase in NK cell activity has been associated with less depressive symptoms (Cruess et al., 2005). Low CD4+ lymphocyte counts and high viral load has been associated with increased susceptibility to depression (Ickovics et al., 2001). We recently determined that HIV infection may dysregulate serotonin transmission in the brain thereby increasing the risk of depression (Hammoud et al., 2010).

Depression is associated with faster disease progression and higher mortality (Cook et al., 2004; Ickovics et al., 2001; Leserman et al., 2002; Whetten et
al., 2006). Depressed patients generally adhere less to their medication regimen than non-depressed patients (DiMatteo, Lepper, & Croghan, 2000; Yun, Maravi, Kobayashi, Barton, & Davidson, 2005). Higher medication adherence is associated with better virologic outcome, greater increase in CD4 lymphocyte counts, lower rates of hospitalization, and decreased rates of AIDS-related mortality (Cruess et al., 2005; Paterson et al., 2000). Among patients with poor adherence, mortality rates are higher in those with depressive symptoms than in those without depressive symptoms (Lima et al., 2007). These adherence-independent effects of depression may result from direct effects of the immune system on depression, as well as depression-related behavioral mechanisms. Depression in HIV can be effectively treated with psychotropic medication, psychological interventions, and by incorporating cognitive-behavioral components (Sherr et al., 2011; Treisman & Angelino, 2004).

**Cognitive Impairment in Persons with HIV/AIDS**

Recent reports have shown a consistent association between depression and incident cognitive impairment in HIV (Sevigny et al., 2004). HIV-associated neurocognitive disorders (HAND) have varying degrees of severity of neurocognitive impairment and include asymptomatic neurocognitive impairment, minor neurocognitive disorder and severe HIV-associated dementia (Antinori et al., 2007).

Prior to cART the annual rate of dementia was about 7% in patients with AIDS (McArthur et al., 1993). Although cART has reduced the incidence of dementia, the prevalence of HIV-associated dementia appears to be increasing due to increased
survival (Nath et al., 2008). In the cART era, the annual incidence of dementia has decreased by about 15-50% (McArthur, Sacktor, & Selnes, 1999), although prevalence of neurocognitive impairment remains high. Prevalence estimates of HAND range between 5-60% (Joska, Gouse, Paul, Stein, & Flisher, 2010). cART use is associated with improvement in cognition. A higher concentration of anti-HIV medication in the CNS is hypothesized to be the primary modulator of beneficial neurological response (McArthur, Brew, & Nath, 2005). On the basis of ability of HIV medications to reduce the CSF HIV RNA to undetectable levels and improve cognition, some drugs have been described as being more neurologically active than others (Marra et al., 2003; Polis et al., 2003; Price et al., 1999; Sidiis et al., 1993).

Before cART was introduced, CSF HIV RNA levels were shown to be positively correlated with the severity of dementia in HIV (Brew, Pemberton, Cunningham, & Law, 1997; McArthur et al., 1997). With the introduction of HAART this relationship is less robust (Antinori et al., 2007; McArthur et al., 2004). It has been hypothesized that this finding may be a result of the altered immune activations and CSF cell traffic that mediate CSF treatment effects in persons who have failed cART therapy. Incomplete viral suppression in persons who have failed therapy is often accompanied with reduced immune activation and may reduce cell traffic and result in lower CSF HIV-1 RNA levels (Spudich, Lollo, Liegler, Deeks, & Price, 2006).

**Immune Mediated Depression**

Several bodies of evidence suggest that inflammatory cytokines released through inflammatory responses may be involved in the pathobiology of major depression
(Anisman et al., 2008; Cook et al., 2004; Dantzer et al., 2008; Lima et al., 2007).
Elevated inflammatory cytokines, chemokines, inflammatory mediators and adhesion molecules have been demonstrated in persons with major depression regardless of wellness state in comparison to non-depressed persons (Cook et al., 2004; Dantzer et al., 2008; G. E. Miller, Rohleder, & Cole, 2009). Treatment with inflammatory stimuli such as INF-α, have been shown to induce depressive symptoms in both the acute and chronic phase (Yirmiya, 1996; Zorrilla et al., 2001). Anti-inflammatory agents and chemokine antagonists have been shown to increase antidepressant response or reduce depressive symptoms (Brydon, Harrison, Walker, Steptoe, & Critchley, 2008; Reichenberg et al., 2001).

There is also compelling evidence suggesting that activated cells and inflammatory cytokines can traverse into the brain where they activate depression pathways (Anisman et al., 2008; Capuron et al., 2003; Dantzer et al., 2008; D’Mello et al., 2009; Felger et al., 2007; A. H. Miller et al., 2009; Quan & Banks, 2007; Raison et al., 2009; Weidenfeld & Yirmiya, 1996). Research has demonstrated elevated INF-α, TNF-α, IL-6 and MCP-1 in the CSF of persons who developed depression on interferon treatment for hepatitis C (Muller et al., 2006).

**Cerebrospinal Fluid Viral Escape**

Higher CNS penetrating effectiveness of cART is associated with better CSF viral suppression (Cusini et al., 2013). However a few recent reports have described persistent detectable CNS virus despite suppression of plasma viral replication, known as CSF viral escape (Canestri et al., 2010; Eden et al., 2010; Peluso et al.,
2012). CSF viral escape is defined as detectable CSF HIV RNA in the presence of clinically undetectable plasma levels, or CSF HIV RNA concentration ≥1 log greater than plasma HIV RNA concentration. These reports on CSF viral escape, which have been based on small sample sizes, estimate the prevalence of CSF viral escape at about 10%, although not necessarily designed as prevalence estimate studies.

**Proposed Dissertation**

We propose to investigate if lower CNS penetrating antiretroviral drugs (low CPE of cART) are associated with increased depression and CSF virologic failure independent of cognitive impairment. A conceptual framework for this dissertation is provided in *Figure 2-1*. We will utilize the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) prospective cohort study data for the purposes of this research. We will assess the accuracy of the CPE score in predicting the presence of detectable CSF HIV RNA at a threshold of 50 copies/ml.

In associating CPE of cART to immune medicated depression, our auxiliary hypotheses remains that the CPE score is a surrogate of CNS or CSF HIV activity, and that low CNS penetrating drugs will result in higher residual CNS HIV activity and thus more risk for immune mediated depression in persons with HIV. If the CPE score accurately predicts detectable CSF HIV RNA, it confirms the CPE score a surrogate for the presence of detectable CSF HIV RNA. If the CPE score does not accurately predict detectable CSF HIV RNA, we will develop a new risk score as a surrogate to accurately predict detecting HIV RNA in the CSF.
We will examine if detectable CSF HIV RNA is associated with increased risk of depression which we hypothesize to be partially immune mediated. We will also evaluate the association between depression and CSF viral escape hypothesizing that depression is associated with higher rates of CSF viral production because of alteration of the immune system in persons who are depressed.
Table 2-1. Central Nervous System Penetration Effectiveness Rankings

<table>
<thead>
<tr>
<th>Antiretroviral Drug Class</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside analogue reverse transcriptase inhibitors</td>
<td>Zidovudine</td>
<td>Abacavir</td>
<td>Didanosine</td>
<td>Tenofovir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emtricitabine</td>
<td>Lamivudine</td>
<td>Zalcitabine</td>
</tr>
<tr>
<td>Nonnucleoside analogue reverse transcriptase inhibitors</td>
<td>Nevirapine</td>
<td>Delavirdine</td>
<td>Efavirenz</td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Indinavir/ritonavir</td>
<td>Darunavir/ritonavir</td>
<td>Atazanavir/ritonavir</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fosamprenavir/ritonavir</td>
<td>Fosamprenavir</td>
<td>Saquinavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indinavir</td>
<td>Atazanavir/ritonavir</td>
<td>Saquinavir/ritonavir</td>
</tr>
<tr>
<td>Entry/fusion inhibitors</td>
<td>Maravirov</td>
<td></td>
<td></td>
<td>Enfuvirtide</td>
</tr>
<tr>
<td>Integrase strand transfer inhibitors</td>
<td>Raltegravir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Larger numbers reflect estimates of better penetration or effectiveness in the central nervous system (eg, a ranking of 4 indicates the best penetration or effectiveness). Based on data from Abstract 172.

Figure 2-1. Conceptual Framework for the Association Between CNS penetration of Antiretroviral Therapy and Depression, and CSF Virologic Failure

CPE: Central Nervous System Penetration Effectiveness; CSF: Cerebrospinal Fluid; HIV: Human Immunodeficiency Virus
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CHAPTER 3

THE CEREBROSPINAL FLUID HIV RISK SCORE FOR
ASSESSING CENTRAL NERVOUS SYSTEM ACTIVITY IN
PERSONS WITH HIV
ABSTRACT

**Background:** Detectable cerebrospinal (CSF) HIV ribonucleic acid (RNA) is associated with central nervous system (CNS) complications including neurocognitive impairment and depression. Routine monitoring of CSF HIV RNA presents a valuable key to reducing HIV CNS complications. However the lumbar puncture procedure poses a resource utilization challenge. We developed a prediction model to estimate the risk of detectable CSF HIV RNA (threshold >50 copies/ml) that will help identify which patients might benefit most from CSF monitoring.

**Methods:** The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) prospective cohort is an ongoing 6-Center, US-based study. All 1,053 participants on combination antiretroviral therapy (cART) at study entry (2004-2007) were evaluated. We applied points to the final prediction model to develop a detectable CSF HIV Risk Score.

**Results:** Plasma HIV RNA, CNS Penetration Effectiveness (CPE), duration of cART, adherence, race and depression status were retained as predictors of CSF HIV RNA. The CSF HIV Risk Score ranges from 0 to 42 points, displaying good calibration, Hosmer-Lemeshow p-value=0.85, and discrimination corrected for optimism, c-statistic=0.84. The CSF HIV Risk score has mean [standard deviation (SD)] of 15.4 (7.3). At risk scores >25, the observed probability of detecting CSF HIV RNA was at least 42.9% [95% Confidence Interval (CI): 36.6, 49.6]. For each point increase in risk score, the odds of detecting CSF HIV RNA increases by 26% [Odds Ratio (OR)= 1.26, 95%CI 1.21-1.31; \( P<0.01 \)].
**Conclusion:** The CSF HIV Risk Score predicts detection of HIV RNA in the CSF. An elevated risk score suggests which patients will benefit from CSF HIV RNA monitoring. The risk score presents an advance in HIV management and monitoring of CNS effects of HIV, providing a potentially useful tool for clinicians.
BACKGROUND

The introduction of combination antiretroviral therapy (cART) has improved survival and reduced opportunistic infections in persons infected with HIV (Brodt et al., 1997). Combination antiretroviral therapy has also been associated with a greatly reduced incidence and phenotypic severity of HIV-associated neurocognitive disorder (HAND), although milder forms of HAND have seen an increase in prevalence (McArthur, 2004; Sacktor et al., 2002; Woods, Moore, Weber, & Grant, 2009). Even though cART use improves cognition, a significant percentage of patients develop new cognitive impairment or depression during treatment (Robertson et al., 2007). This is important because neurocognitive impairment and depression are both associated with poor HIV outcomes and substantially worse survival (Heaton et al., 2004; Ickovics et al., 2001; Tozzi et al., 2005).

HIV infection in the CNS may be associated with glial and endothelial activation resulting in inflammatory and degenerative insults that lead to neuronal injury and neurocognitive impairment (Christo, Greco, Aleixo, & Livramento, 2007; Letendre, Ellis, Ances, & McCutchan, 2010; Spudich et al., 2011). HIV viral replication in the CSF is hypothesized to be clinically relevant pertaining to neurologic and psychiatric complications of HIV. Residual viral replication in the CSF in patients with undetectable plasma HIV RNA, called CSF viral escape, is estimated to occur in over 10% of patients and considered clinically relevant by several groups across the United States and Europe (Canestri et al., 2010; Eden et al., 2010; Letendre et al., 2010). CSF viral escape has been associated with HAND,
depression and neurological deficits in HIV (Garvey, Everitt, Winston, Mackie, & Benzie, 2009; Letendre et al., 2010; Spudich et al., 2011).

Recent findings suggest CSF testing to examine residual viral activity, immune activation and neural damage in managing HAND (Schouten, Cinque, Gisslen, Reiss, & Portegies, 2011). The 2011 European AIDS Clinical Society also provides guidelines for measuring CSF HIV RNA levels as a component of their clinical strategy for managing HAND (European AIDS Clinical Society, 2012). The Mind Exchange Program which consists of 66 clinicians from 30 countries, in a recent Consensus Report recommends CSF testing for HIV RNA in persons with suspected or demonstrated neurocognitive impairment (Mind Exchange Working Group, 2013).

Some antiretroviral drugs are hypothesized to be more neurologically active than others based on their ability to penetrate the CNS and effectively suppress virus replication as reflected by reductions in CSF HIV RNA (Polis et al., 2003; Price et al., 1999). Improvement in cognition with higher CNS penetrating drugs and suppression of CSF HIV RNA are hypothesized to be primary modulators of favorable neurological response in HIV (Cysique, Waters, & Brew, 2011; Ellis et al., 2002). CSF analysis is useful to assess the activity of HIV in the CNS reflected by detectable HIV RNA (Schouten et al., 2011). Poor cART penetration of the blood-brain barrier and active efflux systems that reduce parenchymal concentration of cART, may allow HIV replication to continue in the CNS despite peripheral suppression (Strazielle, Khuth, & Ghersi-Egea, 2004).
Because lumbar punctures may pose a resource utilization challenge in HIV clinics worldwide and is not without risks, we developed an algorithm to predict detectable CSF HIV RNA during HIV treatment using readily attainable clinical and demographic data that would be useful for clinical management of HIV. We accomplished this using data from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort.

**METHODS**

**Study design and Patients**

CHARTER is a 6-Center, US-based prospective, observational study started in 2004 and designed to comprehensively assess a representative US clinical population of persons who were HIV-seropositive (Heaton et al., 2010). There were no general exclusion criteria except the inability to consent to participation in study assessments. CHARTER aimed to evaluate the changing presentation of HIV neurological complications in the context of cART. Study sites include Johns Hopkins University, Baltimore, MD; Icahn School of Medicine at Mt. Sinai, New York, NY; University of California, San Diego, CA; University of Texas, Galveston, TX; University of Washington, Seattle, WA; and Washington University, St. Louis, MO. The Institutional Review Board (IRB) at each study site or the Western IRB approved the study.

Participants were included in our analyses if there were on cART at the time of study entry. We analyzed data from 1,053 out of 1,561 CHARTER participants who were currently on cART at study entry between 2004 and 2007. Participants
underwent extensive evaluation including HIV and treatment history verified by medical records, physical examination, lumbar puncture, and venipuncture.

**Diagnostic Predictors of CSF HIV**

Potential predictors included patient demographics, HIV treatment related data, including current and nadir CD4+ T-cell count, plasma and CSF HIV RNA levels, number of medications and CNS Penetration Effectiveness (CPE) score of current and past cART regimen which is an estimate of the CNS penetration of cART (Letendre et al., 2010), duration and type of cART regimens (protease inhibitor vs. non-nucleoside reverse transcriptase inhibitor based regimen), duration of HIV seropositivity, and medication adherence which was assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire (Chesney et al., 2000).

Other predictors included the Global Deficit Score, a validated measure that derives from the standardized, comprehensive neurocognitive assessment and summarizes overall functioning across 7 cognitive abilities (Carey et al., 2004), major depressive episode within the last 30 days assessed by Diagnostic Statistical Manual (DSM-IV) criteria (American Psychiatric Association, 2000), Beck Depression Inventory (BDI) (Steer, Clark, Beck, & Ranieri, 1999), history of opportunistic infection and HCV seropositivity. Information on illicit substance use and abuse was obtained by the Composite International Diagnostic Interview for DSM-IV.

**Outcome**
The outcome was the presence of CSF HIV RNA at a threshold of 50 copies/mL. Both CSF and plasma HIV RNA levels were determined by commercial ultrasensitive reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostic Systems, Indianapolis, Indiana).

**Statistical Analysis**

The population characteristics were examined using summary statistics. We fit a stepwise backwards multivariable logistic regression model (Royston, Moons, Altman, & Vergouwe, 2009), the outcome being detectable CSF HIV RNA. Predictors associated with detectable CSF HIV virus were retained at a significance level of 0.157 which equates to the Akaike information criterion (AIC) for selection of a single predictor (Sauerbrei, Royston, & Binder, 2007). Selection of predictors at this level rather than conventional significance levels reduces selection bias thus preventing overestimated regression coefficients and diminishes optimism from overfitting of the data, which results in poor prediction in independent data.

Transformed continuous predictor variables were compared to linear forms to determine the best-fitting functional forms to be included in the final model (Royston et al., 2009; Sullivan, Massaro, & D'Agostino RB, 2004). Continuous forms of all variables were preferentially fitted in regression models because of the advantage of creating robust regression models compared to using relatively arbitrary cut-points of categorization (Sauerbrei et al., 2007).

The predictive accuracy of the retained model was assessed and compared by forcing in specific variables and reducing the selected model. Discrimination was assessed by the receiver operator curve (ROC) c-statistic (Hanley & McNeil, 1982), a
measure of chance that the prediction model will assign a higher probability to a patient with detectable CSF HIV RNA compared to a patient without detectable CSF HIV RNA. We assessed model calibration by the Hosmer-Lemeshow test (Hosmer DW, 2000), which compares the observed and predicted probabilities of detectable CSF HIV RNA in various risk classes in the study population.

Internal validation was performed by 5-fold cross-validation and bootstrapping techniques (Royston et al., 2009). To prevent our model from being overly optimistic in future applications, we calculated shrunken estimates by applying the calculated Van Houwelingen and le Cessie heuristic shrinkage estimator (Van Houwelingen & le Cessie, 1990). To enhance the future application of our findings in clinical settings, we utilized the risk score approach to apply points to the final prediction model (Sullivan et al., 2004). We calculated the predicted probability estimates of detectable CSF HIV RNA for the logistic regression model provided by: \( p = 1 / [1 + \exp(-\sum \beta_i x_i)] \) (Sullivan et al., 2004).

We examined the distribution of CSF viral load by risk score category and fit logistic regression models to examine the odds of detectable CSF HIV RNA per 1, 5 and 10 points increase in risk score. Missing data were handled by multivariate imputation using chained equations by linear and augmented logistic regression (Rubin, 1987) imputing the median of 50 values generated from each observation (Donders, van der Heijden, Stijnen, & Moons, 2006). Model checking, diagnostic procedures and sensitivity analyses were performed. Because the CPE score is the current estimate of the extent to which cART penetrates the CNS, we also examined the performance of the CPE score in predicting and discriminating persons with
detectable CSF HIV RNA. Author ERH performed the statistical analysis with Stata Statistical Software: Release 12. (College Station, TX: StataCorp LP).

RESULTS

Demographic and clinical characteristics of participants included in our analysis are displayed in Table 3-1. The mean age was 43.3 years with 78% being male. Whites comprised 39.2%, Blacks 49.7% and Hispanics 12.8% of the population. The mean (SD) duration of cART usage was 20.6 (23.0) months and the mean (SD) duration of HIV seropositivity was 130.1 (72.6) months. Prior diagnosis of opportunistic infection was reported in 14.3% of the study sample, and 13.4% met DSM-IV criteria for current depression. Overall, CSF HIV RNA was detectable (50 copies/ml) in 15.7% (127 of 811).

In multivariable logistic regression analysis, CPE, race, depression, plasma HIV RNA, duration of cART and adherence were retained as predictors of detectable CSF HIV RNA. Five-fold cross-validation of retained predictors showed very good discrimination, with a c-statistic of 0.90 for the full model (Figure 3-1). The calibration plot for the full model demonstrates that predicted probabilities were similar to observed probabilities, Hosmer-Lemeshow p=0.85 (Figure 3-2). Further internal validation by bootstrapping methods correcting for model optimism (e.g., overfitting of data), displayed good discrimination, and a c-statistic of 0.84. Average optimism was 0.074. The mean variance inflation factor, a measure of how predictor variables are correlated, was 1.03. When we examined the performance of the CPE score alone in predicting detectable CSF HIV RNA, we observed a lower
discrimination and calibration performance (c-statistic=0.58, and Hosmer-Lemeshow P=0.008) (*Figures 3-3 and 3-4*).

*Table 3-2* summarizes the development of the CSF HIV Risk Score. The observed predictor variable coefficients were multiplied by the calculated shrinkage factor 0.937 to prevent overfitting if this model should be applied to another population. Model fit due to noise was 6.3%.

The CSF HIV Risk score ranges from 0 to a maximum of 42 points. In our study population, the risk score ranged from 0 to 39 points, mean (SD) of 15.4 (7.3). *Figure 3-5* shows the distribution of the CSF Risk Score. The largest predictor of detectable CSF HIV was plasma HIV RNA, at levels >10,000 copies/ml, contributing 42.9% (18 points) of the maximum possible total risk score.

The predicted probabilities of detectable CSF HIV RNA in persons on cART for various levels of the CSF HIV risk score are displayed in *Table 3-3* and *Figure 3-6*. For example a Black patient (3 points), with plasma HIV RNA of 300 copies/mL (10 points), who is presently depressed (4 points), and is fully adherent to cART regimen (0 points), whose regimen has a total CPE of 9 (6 points) for a duration of 10 months (4 points; total CSF HIV RNA score 27 points) has a 54.3% (95% CI: 46.5, 62.0) probability of having detectable CSF HIV RNA. At risk scores >25, the observed probability of detecting CSF HIV RNA is at least 42.9% (95% CI: 36.6, 49.6).

We observed a dose response association between increasing CSF HIV risk score category and increasing CSF viral load (*Table 3-4, Figure 3-7*). For each point increase on the risk score, the odds of detecting CSF HIV RNA increased by 26% (OR=1.26, 95%CI: 1.21, 1.31; P<0.001) *Figure 3-8*. Likewise, an increase of 5 and 10
points in risk score were associated with a 3-fold increase in odds (OR=3.16, 95%CI: 2.64, 3.79; \( P<0.001 \)), and 9-fold increase in odds (OR=9.99, 95%CI: 6.95, 14.1; \( P<0.001 \)), respectively.

**Sensitivity analyses**

We conducted a sensitivity analysis by developing the CSF HIV Risk Score using only participants with complete data (complete case analysis), \( n=790 \). The same set of predictors was retained as with the multiple imputation approach except “duration of current cART”. We forced “duration of current cART” in the final regression model under the assumption that therapeutic levels of cART need to be attained prior to objective assessment of effectiveness in reducing plasma and CSF HIV RNA. The observed associations and regression coefficients were similar for multiple imputation as with complete case analysis. In comparison, multiple imputation analysis yielded more precise estimates.

**DISCUSSION**

We developed a CSF HIV Risk Score to predict the probability of identifying detectable CSF HIV RNA in persons on cART. This score may provide a practical means to estimate the probability of finding CSF HIV RNA thus providing a meaningful tool to discuss the utility of performing a lumbar puncture. Measures of predicting CSF HIV RNA have not been previously described so our findings contribute significantly to the field and may allow meaningful inferences to be drawn in HIV management.
The CSF HIV Risk Score displayed high predictive accuracy with two robust internal validation techniques; cross-validation performance of 0.9 and bootstrapped performance with correction for optimism of 0.84. This can be interpreted as at least an 84% probability that the CSF HIV Risk score will assign a higher probability of detecting CSF HIV RNA in one patient with positive CSF HIV than in a patient with undetectable CSF HIV RNA.

Our prediction tool may hold promise for clinical management of HIV. It relies on measurements that are readily available, plasma HIV RNA, CPE, duration of current cART regimen, adherence, race and depression status. The mean variance inflation factor of 1.03 suggests no collinearity between predictor variables, an indication that each variable contributes sufficiently and independently towards predicting detectable CSF HIV RNA. To the clinician, this may suggest that addressing modifiable predictors may reduce the risk of persistent detectable CSF HIV RNA that several studies have indicated to be harmful (Letendre et al., 2010; Marra et al., 2009).

At plasma HIV RNA <10,000 copies/ml, each predictor variable in the final regression model contributes significantly to assessing CSF HIV risk. This may suggest that below plasma HIV RNA levels of 10,000 copies/ml, routine monitoring of plasma HIV RNA may not be a sufficient surrogate for estimating CSF HIV activity and supports previous findings of CSF viral escape in persons with undetectable plasma virus (Eden et al., 2010; Peluso et al., 2012).

Although routine plasma HIV RNA monitoring is recommended as standard of care (DHHS, 2011), an increased CSF HIV Risk score may suggest which patients
will benefit from CSF HIV RNA monitoring. Application of this risk score may better focus resources to enable cost-effective monitoring of CNS disease.

When clinical deterioration is noticed in a previously stable patient, the risk score could potentially be applied to provide insight into possible CNS HIV disease activity. Such assessments may necessitate an informed clinical decision to request CSF examination including measurement of HIV RNA, immune activation and viral resistance. The risk score could also be monitored during alteration of therapy. An assessment of the probability of detectable CSF HIV RNA may facilitate measures to alter modifiable predictive factors such as CPE of ART regimen, adherence and depression.

Depression is the most common psychiatric disorder associated with HIV. In persons with HIV disease, depression has been associated with lower CD4+ cell counts, immune activation, and increased mortality in HIV, whereas resolution of depression is associated with increased natural killer cell activity (Cruess et al., 2005; Ickovics et al., 2001). Our findings may suggest that effectively treating depression may potentially reduce the probability of detecting CSF HIV RNA.

Race was identified as a non-modifiable predictor of detectable CSF HIV RNA with Blacks and Hispanics displaying significantly higher risk. Higher risk of HIV/AIDS acquisition has been associated with Blacks and Hispanics (Centers for Disease Control and Prevention, 2006). Reasons for racial HIV disparities are complex and include differences in access to care and utilization of cART, differences in clinical response to cART and proposed genetic variations including the CCR5 and CCLC3 genes (Gebo et al., 2005; Samson et al., 1996; Tedaldi, Absalon,
Thomas, Shlay, & van den Berg-Wolf, 2008). Application of knowledge about the overall risk of detectable CSF HIV RNA may help addresses these disparities.

We present the CSF HIV Risk Score as a clinical tool to help improve medical management of HIV. However, its utility may extend beyond the goal of suppressing HIV replication and apply to managing HAND. A recent algorithm for early detection of HAND identified age, current CD4 cell count, past CNS HIV-related diseases and current cART duration as predictors (Cysique, Murray, Dunbar, Jeyakumar, & Brew, 2010). The CSF HIV Risk Score may help to focus research into how CSF HIV RNA, a proximal factor in the causal pathway to developing HAND, may affect HIV outcomes.

The CSF HIV Risk Score may offer an insight into longitudinal cognitive changes when applied to already available and prospective epidemiologic data. It is conceivable that repeated monitoring of the CSF HIV Risk score to ensure low scores are maintained would lead to better neurocognitive and neuropsychiatric HIV outcomes. We caution however, against the use of the risk score as a surrogate endpoint in clinical trials. This Score may help identify patients for whom a CSF examination might be most informative.

A limitation to the utilization of this risk score is that depression was assessed by DSM-IV criteria. This criterion for depression may not be readily available to HIV care providers. In our population, persons who met diagnostic DSM-IV criteria for depression had a mean (SD) BDI II score of 25.0 (10.8). We did not evaluate the effect of current substance and alcohol use disorders because a
diagnosis of current DSM-IV substance or alcohol use disorder was infrequent, 0.9% and 0.8% of the population, respectively.

In this analysis, we were able to ascertain a temporal relationship between the cART use and detectable CSF HIV because all participants were on cART prior to CSF evaluation. The type and duration of cART use was determined from patient medical records at the time of enrollment and unlikely to be misclassified. Our study design also enhances the use of the risk score as a tool to make an assessment of current cART at the time of evaluation, which in essence is the utility of prognostic and diagnostic models. In future, the risk predicted by the CSF HIV Risk Score needs to be compared to observed risks in another population for external validation. Its use in other populations may require calibration.

Strengths of this study include the large sample size of patients with CSF HIV RNA measurement. Approximately 15% of the study population had detectable CSF HIV RNA. Use of augmented multiple imputations allowed utilization of the entire study cohort data. Because of a low ratio of retained predictors to number of outcomes, 1:26, it ensured a good model fit with only 6.3% fit due to noise, thereby reducing overoptimism in its application in other populations.

In conclusion, the CSF HIV Risk Score represents a possible advance in HIV management and monitoring of CNS effects of HIV, providing a potentially useful tool for clinicians. Continuous CSF HIV Risk Score monitoring with the necessary treatment and evaluation follow-up, may help prevent HIV-related neurological and psychiatric complications and improve HIV outcomes.
### Table 3-1. Characteristics of Individuals on Combination HIV Therapy at Study Entry in the CNS HIV Antiretroviral Research (CHARTER) Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N)</th>
<th>n (%)</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1053</td>
<td></td>
<td>44.3 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1053</td>
<td></td>
<td>822 (78.1)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>1053</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>414</td>
<td></td>
<td>12.6 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>504</td>
<td></td>
<td>120.0 (29.0-218.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Other</td>
<td>135</td>
<td></td>
<td>418.5 (248.0-610.0)</td>
<td></td>
</tr>
<tr>
<td>Education, years</td>
<td>1053</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ Nadir, cells/mm3</td>
<td>1053</td>
<td></td>
<td>150.6 (147.1)</td>
<td>120.0 (29.0-218.0)</td>
</tr>
<tr>
<td>Current CD4, cells/mm3</td>
<td>1042</td>
<td></td>
<td>458.0 (290.7)</td>
<td>418.5 (248.0-610.0)</td>
</tr>
<tr>
<td>Log Plasma HIV RNA, copies/mL</td>
<td>1040</td>
<td></td>
<td>2.35 (1.04)</td>
<td>1.70 (1.70-2.70)</td>
</tr>
<tr>
<td>Log CSF HIV RNA, copies/mL</td>
<td>811</td>
<td></td>
<td>1.86 (0.49)</td>
<td>1.70 (1.70-1.70)</td>
</tr>
<tr>
<td>CSF HIV virus present, %</td>
<td>811</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Regimen types</td>
<td>1053</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI based</td>
<td>362</td>
<td></td>
<td>34.4</td>
<td></td>
</tr>
<tr>
<td>PI based</td>
<td>599</td>
<td></td>
<td>56.9</td>
<td></td>
</tr>
<tr>
<td>PI/NNRTI based</td>
<td>54</td>
<td></td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>36</td>
<td></td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Number of HIV drugs</td>
<td>1053</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 drugs</td>
<td>794</td>
<td></td>
<td>75.4</td>
<td></td>
</tr>
<tr>
<td>&gt;3 drugs</td>
<td>259</td>
<td></td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>CNS Penetration</td>
<td>1053</td>
<td></td>
<td>7.3 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Effectiveness</td>
<td>1045</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Medication Adherence, %</td>
<td>1045</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=95</td>
<td>915</td>
<td></td>
<td>87.6</td>
<td></td>
</tr>
<tr>
<td>85-84</td>
<td>46</td>
<td></td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>&lt;85</td>
<td>84</td>
<td></td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>HCV positive</td>
<td>1034</td>
<td></td>
<td>275 (26.6)</td>
<td></td>
</tr>
<tr>
<td>Total BDI</td>
<td>1044</td>
<td></td>
<td></td>
<td>13.9 (10.8)</td>
</tr>
<tr>
<td>Current DSM-IV Depression diagnosis within last 30 days, n (%)</td>
<td>1049</td>
<td>140</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>BDI score &gt;14</td>
<td>1044</td>
<td></td>
<td>459 (44.0)</td>
<td></td>
</tr>
<tr>
<td>BDI score &gt;16</td>
<td>1044</td>
<td></td>
<td>400 (38.3)</td>
<td></td>
</tr>
<tr>
<td>Lifetime depression</td>
<td>1049</td>
<td></td>
<td>527 (50.2)</td>
<td></td>
</tr>
<tr>
<td>Duration of current treatment, months</td>
<td>1041</td>
<td></td>
<td>20.6 (23.0)</td>
<td></td>
</tr>
<tr>
<td>Duration of HIV infection, months</td>
<td>1050</td>
<td></td>
<td>130.1 (72.6)</td>
<td></td>
</tr>
<tr>
<td>Any Opportunistic Infection</td>
<td>1053</td>
<td>150</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

Table 3-2. Regression Coefficients, Odds Ratios and Development of the CSF HIV Risk Score\(^\d\) in CHARTER Cohort.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Odds Ratio (95% CI)</th>
<th>( P ) value</th>
<th>Shrunken* regression coefficient ( \beta_i )</th>
<th>Category</th>
<th>Reference value ( W_{ij} ) (midpoint)</th>
<th>( \beta_i ) (( W_{ij}-W_{i\text{Ref}} ))</th>
<th>Risk score ((\beta_i \times [(W_{ij}-W_{i\text{Ref}})]/B'))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPE</td>
<td>-0.266</td>
<td>0.77 (0.67, 0.88)</td>
<td>&lt;0.001</td>
<td>0.249</td>
<td>≥10</td>
<td>12 (( W_{1\text{Ref}} ))</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-9</td>
<td>7</td>
<td>1.245</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;5</td>
<td>4</td>
<td>1.992</td>
<td>9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1</td>
<td>1</td>
<td></td>
<td>White</td>
<td>0</td>
<td>0 (( W_{2\text{Ref}} ))</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black</td>
<td>0.593</td>
<td>1.81 (1.06, 3.09)</td>
<td>0.02</td>
<td>Black</td>
<td>1</td>
<td>0.556</td>
<td>3</td>
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<tr>
<td>Hispanic and Other</td>
<td>0.875</td>
<td>2.39 (1.16, 4.95)</td>
<td>0.02</td>
<td>Hispanic and Other</td>
<td>1</td>
<td>0.820</td>
<td>4</td>
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<tr>
<td>Current depression</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1.00</td>
<td></td>
<td>No</td>
<td>0</td>
<td>0 (( W_{3\text{Ref}} ))</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>0.808</td>
<td>2.25 (1.18, 4.28)</td>
<td>0.01</td>
<td>Yes</td>
<td>1</td>
<td>0.757</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;95%</td>
<td>1</td>
<td>1.00</td>
<td></td>
<td>95-100</td>
<td>97.5 (( W_{4\text{Ref}} ))</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>85-95%</td>
<td>0.584</td>
<td>1.79 (0.67, 4.79)</td>
<td>0.23</td>
<td>85-94</td>
<td>89.5</td>
<td>0.547</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&lt;85%</td>
<td>0.599</td>
<td>1.82 (0.90, 3.68)</td>
<td>0.10</td>
<td>&lt;85</td>
<td>80.0</td>
<td>0.561</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Plasma RNA, copies/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>1.584</td>
<td>4.88 (3.91, 6.09)</td>
<td>&lt;0.001</td>
<td>1.486</td>
<td>&lt;1.699</td>
<td>1.699 (( W_{5\text{Ref}} ))</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50-199</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.699-2.299</td>
<td>1.999</td>
<td>0.446</td>
<td>2</td>
</tr>
<tr>
<td>200-9,999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.301-3.999</td>
<td>3.150</td>
<td>2.156</td>
<td>10</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;4.0</td>
<td>5.627</td>
<td>3.928</td>
<td>18</td>
</tr>
<tr>
<td>Current cART months</td>
<td>-0.011</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.07</td>
<td>0.010</td>
<td>&gt;36</td>
<td>75 (( W_{7\text{Ref}} ))</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHARTER: CNS HIV Anti-Retroviral Therapy Effects Research; CPE: CNS Penetration Effectiveness score 2010; cART: Combination antiretroviral therapy; 95% CI: 95% confidence interval.\(^\d\)Under the points system, meaningful categories of predictors were created and the distance from a chosen reference category was determined in regression units. Integer points were assigned to each level of predictor and the risk estimate was determined from total points assigned by a reference table (30). Points were rounded to the next integer.
*Regression coefficients were multiplied by a shrinkage factor of 0.937. †B: Constant for point system or the number of regression units that will correspond to one point. The constant reflects the risk of detecting CSF HIV RNA associated with the study population mean duration on cART, 20.6 months: \( B = 20.6 \times 0.011 = 0.227. \)
Table 3-3. Predicted probabilities of detectable CSF HIV RNA (>50 copies/ml) by the CSF HIV Risk Score in Persons on Combination Antiretroviral Therapy, CHARTER Study, N=811

<table>
<thead>
<tr>
<th></th>
<th>CSF HIV Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Predicted probability (%)</td>
<td>0.24</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.11, 0.53)</td>
</tr>
</tbody>
</table>

Abbreviations: CHARTER: CNS HIV Anti-Retroviral Therapy Effects Research; CSF: Cerebrospinal Fluid; 95% CI: 95% Confidence Interval; RNA: Ribonucleic Acid; Data are predicted probabilities of detectable CSF HIV RNA (95% Confidence Interval) for persons on combination antiretroviral therapy. Odds ratio per increase in risk score; 1-point increase (OR=1.26, 95%CI: 1.21, 1.31; P<0.001); 5-point increase (OR=3.16, 95%CI: 2.64, 3.79; P<0.001), and 10-point increase (OR=9.99, 95%CI: 6.95, 14.1; P<0.001)
**Table 3-4.** Distribution of CSF Viral Load by CSF HIV Risk Score Category in Persons With HIV, CHARTER Study, N=811

<table>
<thead>
<tr>
<th>Category (C)</th>
<th>Risk Score category</th>
<th>N</th>
<th>Log10 CSF viral load</th>
<th>P-value* for comparison of CSF HIV Risk Score categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>1</td>
<td>0-10</td>
<td>217</td>
<td>0.1099</td>
<td>0.4146</td>
</tr>
<tr>
<td>2</td>
<td>11-20</td>
<td>404</td>
<td>0.2716</td>
<td>0.6800</td>
</tr>
<tr>
<td>3</td>
<td>21-30</td>
<td>145</td>
<td>1.4934</td>
<td>1.1495</td>
</tr>
<tr>
<td>4</td>
<td>31-39</td>
<td>45</td>
<td>2.7313</td>
<td>1.2672</td>
</tr>
</tbody>
</table>

Abbreviations: CHARTER: CNS HIV Anti-Retroviral Therapy Effects Research; CSF: Cerebrospinal Fluid.
Figure 3-1. Discrimination plot of the CSF HIV Risk Score: CHARTER Study

CHARTER: CNS HIV Anti-Retroviral Therapy Effects Research; The discrimination plot shows the plot of Sensitivity vs. 1-Specificity of CSF HIV Risk Score indicated by the curved line. The diagonal line shows the non-informative line where sensitivity is equal to specificity. The area under the curve represents the discriminative ability of the test to correctly differentiate between 2 individuals, one with detectable CSF HIV RNA and the other without detectable CSF HIV RNA.
**Figure 3-2** Calibration plot of the CSF HIV Risk Score, CHARTER data

CHARTER: CNS HIV Anti-Retroviral Therapy Effects Research; The x-axis shows the risk of detectable CSF HIV RNA as predicted by the CSF HIV Risk Score. The y-axis shows the observed risk in the CHARTER cohort. Circles represent a risk class with corresponding predicted and observed risk. The solid line represents perfect agreement. The Hosmer-Lemeshow statistic tests whether predicted and observed risks differ significantly across classes.
**Figure 3-3.** Discrimination plot of the CNS Penetration Effectiveness (CPE) Score for Predicting Detectable CSF HIV RNA

The discrimination plot shows the plot of Sensitivity vs. 1-Specificity of CPE Score indicated by the curved line. The diagonal line shows the non-informative line where sensitivity is equal to specificity. The area under the curve represents the discriminative ability of the test to correctly differentiate between 2 individuals, one with detectable CSF HIV RNA and the other without detectable CSF HIV RNA.
**Figure 3-4.** Calibration Plot of the CNS Penetration Effectiveness (CPE) Score for Predicting Detectable CSF HIV RNA

The x-axis shows the risk of detectable CSF HIV RNA as predicted by the CPE Score. The Y-axis shows the observed risk in the CHARTER cohort. Circles represent a risk class with corresponding predicted and observed risk. The solid line represents perfect agreement. The Hosmer-Lemeshow statistic tests whether predicted and observed risks differ significantly across classes.
Figure 3-5. Distribution of the CSF HIV Risk Score

CHARTER: CNS HIV Anti-Retroviral Therapy Effects Research
Figure 3-6. Predicted Probabilities and 95% Confidence Intervals of Detectable CSF HIV RNA by the CSF HIV Risk Score

Predicted Probabilities and 95% Confidence Intervals of Detectable CSF HIV RNA by the CSF HIV Risk Score
Figure 3-7. Distribution of CSF HIV RNA Viral Load by category of CSF HIV Risk Score, CHARTER Study, N=811

CHARTER: CNS HIV Anti-Retroviral Therapy Effects Research; *P<0.001 for CSF Risk Score category 2 vs. categories 3 and 4; **P<0.001 for CSF Risk Score category 3 vs. categories 1, 2 and 4; ***P<0.001 for CSF Risk Score category 4 vs. 1, 2 and 3.
**Figure 3-8.** Odds Ratios for the Association between Change in CSF HIV Risk Score and Detectable CSF HIV RNA, N=811

Odds ratios and 95% Confidence Intervals for 1, 5 and 10 point increase in the CSF HIV Risk Score
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74
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doi:10.1097/QAD.0b013e328355e6b2

doi:10.1097/01.aids.0000060391.18106.95


doi:10.1097/QAD.0b013e32828e4e27


doi:10.1080/13550280290049615


doi:10.1002/sim.3148


CHAPTER 4

PERSISTENT CSF HIV RNA, BUT NOT PLASMA HIV RNA IS ASSOCIATED WITH INCREASED RISK OF NEW-ONSET MODERATE-TO-SEVERE DEPRESSIVE SYMPTOMS
ABSTRACT

Background: Major depressive disorder is the most common neuropsychiatric complication in persons with HIV and is associated with worse clinical outcomes. It is unknown whether detectable CSF HIV RNA is associated with an increased risk of new-onset depression.

Methods: The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort is a six-center US-based prospective observational study with bi-annual follow-up of 674 participants (among the original baseline sample of 1,561 participants). We fit linear mixed models and discrete-time survival models to evaluate trajectories of Beck Depression Inventory (BDI) II scores, and the incidence and risk of new-onset depression using BDI cut-off ≥17 (moderate-to-severe depressive symptoms) among participants followed through 2,496 person-months who were free of depression at study entry and had a minimum of three CSF examinations during follow-up, (N=223), over 823 observations.

Results: Detectable CSF HIV RNA (threshold ≥50 copies/ml) at any visit was associated with a 4.7-fold increase in new-onset depression at subsequent visits adjusted for plasma HIV RNA and treatment adherence (HR=4.76, 95% CI: 1.58-14.3; \(P=0.006\)). BDI scores were 2.53 points higher (95% CI: 0.47-4.60; \(P=0.02\)) over 6 months if CSF HIV RNA was detectable at a prior study visit in fully adjusted models including age, sex, race, education, plasma HIV RNA, duration and adherence of cART, and lifetime depression diagnosis by DSM-IV criteria.

Conclusions: Persistent CSF HIV RNA, but not plasma HIV RNA is associated with an increased risk for new-onset depression. Further research evaluating the role of immune activation and inflammatory markers will improve our understanding of
this association. We speculate that depression may be a surrogate of ongoing CNS inflammation and injury.
BACKGROUND

Major Depressive Disorder (MDD) is the most common neuropsychiatric disorder associated with HIV (Zanjani, Saboe, & Oslin, 2007). In the United States, the prevalence of MDD in HIV remains high, estimated between 22-46%, even with combination antiretroviral therapy (cART) use (Penzak, Reddy, & Grimsley, 2000). Globally, MDD is a leading cause of disability adjusted life years (DALYs) (Murray et al., 2013). Compared to the general US population with an estimated 9% depression prevalence (Centers for Disease Control and Prevention (CDC), 2010), persons with HIV bear some of the highest burden of depression-associated disability.

MDD is associated with negative outcomes such as low productivity and medication non-compliance, and with comorbidities such as cardiovascular disease, stroke, diabetes, substance use and suicidality (Grenard et al., 2011; Hees, Koeter, & Schene, 2013; G. E. Miller, Stetler, Carney, Freedland, & Banks, 2002; Pacek, Martins, & Crum, 2012; Sanchez-Gistau et al., 2012). MDD in HIV is associated with decreased adherence to cART, poor virologic outcomes, faster disease progression, increased hospitalization rates and higher mortality (Cook et al., 2004; Ickovics et al., 2001; Kacanek et al., 2010).

There is increasing evidence implicating the activation of inflammatory pathways in MDD through innate and adaptive immune responses (A. H. Miller, Maletic, & Raison, 2009). Elevated levels of plasma and CSF pro-inflammatory cytokines such as IL-6, TNF-α and IL-1b are associated with MDD (Raison et al., 2009). Hepatitis C treatment with interferon has been shown to be associated with CNS inflammatory response and depression. Elevated pro-inflammatory cytokines are associated with development of chronic diseases like diabetes and
cardiovascular diseases (G. E. Miller et al., 2002; Wellen & Hotamisligil, 2005), further suggesting a shared pathogenesis between MDD and chronic disease.

Evidence suggests that a new diagnosis of HIV can lead to onset of depression (Jin et al., 2006), while the progression of HIV further increases the risk of MDD (Lyketsos et al., 1996). Furthermore, synergistic mechanisms between major MDD and HIV may be related to stress and immune dysfunction (Cruess et al., 2005; Evans et al., 2002), with HIV making MDD worse, and MDD in turn making HIV worse.

HIV replication creates an inflammatory environment through activation of the innate and adaptive immune systems (Boasso et al., 2008; Catalfamo et al., 2008). Chronic exposure to inflammatory mediators such as type I IFN is associated with dysregulation of T-cell homeostasis mediated by homeostatic cytokines such as IL-7, and is linked to decreased HIV survival (Boasso et al., 2008; Herbeuval et al., 2005).

Because HIV RNA levels are the main drivers of CD8 T-cell proliferation (Catalfamo et al., 2008), coupled with increasing evidence on the role of inflammation in the pathogenesis of MDD, we hypothesized that detectable levels of HIV RNA in the CSF would be associated with increased risk of new-onset moderate-to-severe depressive symptoms. We evaluated this using data from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort, which uniquely affords bi-annual CSF examinations during follow-up.
METHODS

Study design and Participants

We analyzed data from 674 participants enrolled between 2004 and 2007, and followed through 2009 in the longitudinal arm of the CHARTER study (Heaton et al., 2010). CHARTER is a six-center, US-based prospective, observational cohort study started in 2004 and designed to comprehensively assess a demographically representative US population of individuals who are HIV-seropositive in clinical care. A total of 1,561 CHARTER participants were recruited for cross-sectional evaluation, with biannual follow-up conducted in 674 participants. CHARTER aims to evaluate the changing presentation of HIV neurological complications in the context of cART. There were no general exclusion criteria except the inability to consent to participation in study assessments. Study sites include Johns Hopkins University, Baltimore, MD; Icahn School of Medicine at Mount. Sinai, New York, NY; University of California, San Diego, CA; University of Texas, Galveston, TX; University of Washington, Seattle, WA; and Washington University, St. Louis, MO. The study was approved by the Institutional Review Board (IRB) or Western IRB for each study site and each participant provided written informed consent.

At study entry, CHARTER participants underwent extensive evaluation including HIV and treatment history verified by medical records, physical examination, neuropsychiatric evaluation, neuropsychological testing, lumbar puncture, and venipuncture (Heaton et al., 2010). Thereafter 674 participants who consented to biannual evaluations were selected to undergo follow-up visits every 6 months as part of the longitudinal study.
These analyses include only participants who had completed at least 3 study visits with successful CSF exam. Because we were interested in calculating incidence of new-onset moderate-to-severe depressive symptoms, we excluded 31 participants with prevalent MDD based on Diagnostic Statistical Manual of Mental Disease (DSM-IV) criteria assessed by the World Health Organization Composite International Diagnostic Interview (CIDI) (Kessler & Ustun, 2004). Participants with prevalent depression who were excluded, had significantly higher mean baseline Beck Depression Inventory (BDI) scores, 26.3 (95% Cl: 22.0-30.6) relative to those without prevalent depression, 12.2 (95% Cl: 10.9-13.6). There were no differences in other covariates between participants excluded and those retained in our analysis (n=223).

Because the risk of new-onset depression associated with detectable CSF HIV RNA is unknown, we hypothesized from clinical experience that persons with detectable CSF HIV RNA would have at least a 2-fold increased risk of depression over 12 months compared to persons without detectable CSF HIV RNA. A study of 20 persons with detectable CSF HIV RNA and 100 with undetectable CSF HIV RNA (1:5 ratio), over 24-month follow-up would have 83% power to detect a relative risk of 2.1, and reject the null hypothesis that the survival curves for persons with detectable CSF HIV RNA is equal to those without detectable CSF HIV RNA at Type 1 error (α) =0.05. Our study had sufficient statistical power to detect such a difference.

Measures
The principal outcome variable was new-onset moderate-to-severe depressive symptoms defined as BDI score ≥17, corresponding to a range of moderate-to-severe clinical depression (Aalto, Elovainio, Kivimaki, Uutela, & Pirkola, 2012).

The main exposure of interest was detection of CSF HIV RNA, threshold ≥50 copies/mL. CSF HIV RNA levels were determined by commercial ultrasensitive reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostic Systems, Indianapolis, Indiana).

The fixed covariates evaluated were patient demographics (age, sex, race, and years of education), self-reported duration of HIV seropositivity and nadir CD4+ T-cell, lifetime history of DSM-IV MDD and HCV seropositivity. We incorporated time-varying covariates assessed at each study visit including cART regimen (protease inhibitor vs. non-nucleoside reverse transcriptase inhibitor based regimen) and duration of cART regimen, CNS penetration effectiveness (CPE 2.0) score of cART which is an estimate of the extent to which antiretroviral drugs affect the CNS (Letendre, Ellis, Ances, & McCutchan, 2010), current CD4+ T-cell count, plasma HIV RNA levels, cognitive impairment assessed by the Global Deficit Score (GDS) (Carey et al., 2004), a summary measure of the standardized comprehensive neurocognitive assessment; and medication adherence assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire (Chesney et al., 2000).

**Statistical analysis**

Population characteristics were examined using summary statistics. To examine the time-varying effect of detectable CSF HIV RNA, we fit discrete-time survival models
to estimate hazard odds ratios between detectable CSF HIV RNA and new-onset moderate-to-severe depressive symptoms (Willett & Singer, 1993).

We also assessed the association between baseline detectable CSF HIV RNA and new-onset moderate-to-severe depressive symptoms. Because protease inhibitor (PI)-based cART has been associated with decreased depression scores (Low-Beer et al., 2000), we examined interactions between lifetime MDD and cART regimen use. We examined interactions between plasma HIV RNA and adherence to cART. Because relatively few endpoints were reached, we fit several discrete-time survival models, increasing the number of covariates adjusted in subsequent models.

To examine the trajectories of BDI scores over time, we fit linear mixed models with random intercepts and robust variance-covariance estimates of the model parameters (Laird & Ware, 1982). We examined the effect of detectable CSF HIV RNA on BDI scores throughout follow-up by fitting interactions with time. We performed a Wald test to check the joint hypothesis that coefficients of the interactions were zero.

We fit the best-fitting functional form of each covariate, performing model checks and sensitivity analysis. Statistical analysis was performed by author ERH with Stata Statistical Software: Release 12. (College Station, TX: StataCorp LP).

RESULTS
The study population comprised 223 persons free of DSM-IV MDD at baseline. The mean age at entry was 44.8 years. Most were male (81.6%), with 44.8% Blacks, 39.5% White and 15.7% Hispanic or other race (Table 4-1). At baseline, 32 (14.4%)
participants had detectable CSF HIV RNA at a threshold of ≥50 copies/ml. Participants with detectable CSF HIV RNA were younger, had higher plasma HIV RNA, were more likely to be on protease inhibitor (PI)-based and lower CPE cART regimen, and to have <95% medication adherence. Participants with detectable CSF HIV RNA were also more likely to have experienced a previous lifetime major depressive episode ($P=0.05$). The prevalence of a lifetime depressive episode among the study population was 46.2%.

**Incidence and Risk of New-onset Moderate-to-Severe Depressive Symptoms**

The overall incidence of new-onset moderate-to-severe depressive symptoms over the 2,496 person-months of follow-up was 9.6 per 1,000 person-months (95% CI: 6.1-14.3) (*Table 4-2*). When CSF HIV RNA was detectable, the incidence of new-onset depression was 19.6 per 1,000 person-months (95% CI: 8.8-43.6), compared to 8.2 per 1,000 person-months when CSF HIV RNA was undetectable (*Figure 4-1*).

The overall 2-year cumulative incidence of new-onset moderate-to-severe depressive symptoms was 15.6% (95% CI: 10.4-22.5) increasing to 20% (95% CI: 8.4—39.1) among those with detectable CSF HIV RNA. Baseline detectable CSF HIV RNA was associated with an 83% increased risk of new-onset moderate-to-severe depressive symptoms although this did not meet criteria for statistical significance (unadjusted RR: 1.83; 95% CI: 0.60-4.82).

The time-varying effect of detectable CSF HIV RNA was associated with a more than 4-fold increased risk of new-onset moderate-to-severe depressive symptoms adjusted for plasma HIV RNA and adherence to cART (adjusted HR: 4.76,
95% CI: 1.58-14.3; P=0.006) (Table 4-3). When further adjusted for lifetime depression, duration of cART and sex, we observed similar associations between detectable CSF HIV RNA and increased risk of moderate-to-severe depressive symptoms (Table 4-3). There was no interaction between plasma HIV RNA and adherence.

**Trajectories of Beck Depression Inventory (BDI) II scores**

The mean BDI score at study entry for persons with detectable CSF HIV RNA who were free of MDD was lower, 10.5 (SD 9.0), compared to when undetectable, 12.5 (SD 10.3), with an adjusted mean difference of -2.99 (95% CI: -6.29—0.31), p=0.08 (Table 4-4). However throughout follow-up, BDI scores for persons with detectable CSF HIV RNA increased, whereas BDI scores decreased when CSF HIV RNA was undetectable in adjusted linear mixed models. (Figure 4-2, Table 4-4). Unlike the findings for CSF HIV RNA, plasma HIV RNA (continuous and categorized: <50, 50-199, 200-9,999, ≥10,000 copies/ml) was not associated with an increase in BDI scores over time.

Detectable CSF HIV RNA measured at 6-month intervals was associated with increasing BDI scores over time (Table 4-5). In linear mixed models, the presence of CSF HIV RNA at a prior study visit was associated with an increase in BDI of 2.5 points (95% CI: 0.47-4.60; P=0.02) during the subsequent 6 months after adjusting for age, sex, race, education, log plasma HIV RNA, nadir and current CD4 count, CPE2.0, current duration and adherence of cART, duration of HIV infection, lifetime DSM-IV MDD, DSM-IV substance and alcohol use disorder, depression diagnosis at prior study visit, cognitive impairment and prior diagnosis of HCV infection.
DISCUSSION

We found that persistent CSF HIV RNA (threshold of 50 copies/ml) is associated with over 4-fold increase in new-onset moderate-to-severe depressive symptoms. Furthermore, persistent CSF HIV RNA is associated with an increase in BDI scores, 2.5 points over 6 months. CSF rather than plasma HIV RNA is associated with new-onset moderate depression and worsening depression scores. These findings lend support to our a priori hypothesis that presence of CSF HIV RNA is associated with increased risk for depression in HIV.

At baseline our study population had 12.2% prevalence of DSM-IV MDD which when compared to HIV depression prevalence estimates of 22-45% (Penzak et al., 2000), is rather low, but is similar to that found in the Multicenter AIDS Cohort Study (MACS) using the Center for Epidemiologic Studies Depression (CES-D) Scale (Lyketsos et al., 1996). This suggests that our study population was not at additional or higher risk of new-onset depression than the general HIV population. In this regard, our reported estimates of the association between detectable CSF HIV RNA and new-onset moderate-to-severe depressive symptoms may be conservative.

The evaluation of trajectories of BDI scores over time allows ascertainment of changes in mood along a continuum. The presence of HIV RNA in CSF is associated with an increasing BDI score over time. Of equal importance is our finding that undetectable CSF HIV RNA is associated with decreasing BDI scores over time (Figure 4-2). Persistent over time, detectable CSF HIV RNA may be a cause of increasingly severe depression.
At baseline, persons with detectable CSF HIV RNA had lower mean BDI scores than persons without detectable CSF HIV RNA at baseline, although not significant. This may argue against the value of concurrent evaluation of CSF HIV RNA to assess depressive symptoms. Rather, it is the persistence of CSF HIV RNA that is associated with increased depressive symptoms. Our findings suggest that over time, baseline knowledge of CSF viral load may provide an estimate of the risk of new-onset moderate-to-severe depressive symptoms.

One proposed mechanism for the increased depression in HIV is HIV-induced CNS inflammation. When the innate and adaptive immune systems are activated, pro-inflammatory cytokines and chemokines potentially may cause MDD and worsening of ongoing diseases states (Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008). In animal studies, intraventricular administration of HIV-1 Tat and HIV-1 gp120 has been associated with increased depressive-like behavior (Barak et al., 2002; Lawson, Kelley, & Dantzer, 2011). HIV-1 Tat and gp120 are associated with increased production of pro-inflammatory cytokines (TNF-a, IL-1b, IL-6) and expression of immunomodulatory enzyme indoleamine 2,3-dioxygenase (IDO), which are associated with depressive-like behavior. Proinflammatory cytokines act on intermediates of cellular function and neurogenesis and may link depression with HIV induced cognitive impairment. This mechanism has been suggested as the link between depression and other chronic diseases such as diabetes and cardiovascular diseases as well as neurodegenerative diseases like Alzheimer and Parkinson disease (Anisman, Merali, & Hayley, 2008; G. E. Miller et al., 2002; Wellen & Hotamisligil, 2005).
Because depression is associated with increased risky behavior such as multiple lifetime sexual partners, sex when intoxicated by drugs or alcohol, sex for money or drugs and decreased medication adherence, all of which increase the risk of HIV transmission (High et al., 2012; Hutton, Lyketsos, Zenilman, Thompson, & Erbelding, 2004; Kacanek et al., 2010), it is important that clinicians and providers be aware of its association with detectable CSF HIV RNA.

Unfortunately, mental health services for persons infected with HIV are still grossly unavailable in high-income countries and much more so in mid-to-low income countries (Chander, Himelhoch, & Moore, 2006; High et al., 2012). Presently there are no recommended guidelines for testing CSF in management of HIV or for that matter depression in HIV. The European AIDS Clinical Society guidelines recommend CSF analysis for resistance patterns when neurocognitive impairment is detected (European AIDS Clinical Society, 2012), but US guidelines do not address CSF monitoring.

The association between depression and persistent CSF HIV RNA may be bidirectional. In this study we did not evaluate whether incident depression was associated with future loss of CSF virologic suppression, an unlikely finding given our approach.

Our findings may suggest a clinical role both for monitoring depressive symptoms through valid and reliable assessment tools, and for CSF viral load testing. Its value might include indicators for changes to cART regimen (including treatment intensification), discussions about adherence to medication, counseling aimed at decreasing HIV risky behavior and change in antidepressant therapy. Depression in HIV can be effectively treated with psychotropic medication,
psychological interventions, and by incorporating cognitive-behavioral components of therapy. In persons with refractory HIV-associated depression, knowledge about presence of CSF HIV RNA might become useful to guide treatment choices for both antidepressant and cART regimen. Further efforts are needed to identify persons who would benefit most from routine CSF HIV viral load testing. Baseline knowledge of CSF viral load alone may provide an estimate of the risk of new-onset depression.

Some limitations to our analyses need to be considered. First, although our prospective study is one of the largest available to assess CSF over time, because of the relatively low prevalence of participants at baseline with detectable CSF HIV RNA without MDD, we were unable to assess a dose response association. Also, the measures of association we report for new-onset moderate-to-severe depressive symptoms have wide 95% CIs. It is conceivable that higher levels of CSF HIV RNA may result in further increases in the incidence and severity of depressive symptoms. Second, we detected CSF HIV RNA at a threshold of 50 copies/ml. New ultrasensitive HIV RNA assays enable lower thresholds of HIV RNA detection and might allow refinement of our findings. The threshold for CSF HIV RNA detection we adopted ensures less risk of misclassification.

Although we accounted for the effect of lifetime substance and alcohol use disorder in these analyses, we did not evaluate the effect of current substance and alcohol use disorder because of the low prevalence of current substance and alcohol use disorder in the sample, 0.9% and 0.8% respectively.

Strengths of our study include the availability of data from HIV participants with at least three CSF tests completed. This allowed us to harness the strength of longitudinal data analysis and robust statistical techniques, adequately accounting
for incomplete observations and correlations between repeated measures thereby providing robust estimates (Laird & Ware, 1982). We utilized CSF HIV testing performed at each follow-up visit and incorporated its time-varying nature. We did not account directly for psychotropic medications received during follow-up. However by adjusting for lifetime MDD and depression at a prior study visit, we indirectly accounted for antidepressant therapy effects any participants may have received.

We assessed depressive symptoms by the BDI, a validated tool with high content and construct validity (Aalto et al., 2012). By assessing outcomes at BDI score of ≥17, we captured moderate-to-severe depressive symptoms while excluding mild symptoms. Our approach results in less potential misclassification of depression and helps to ensure that our outcome is more likely to represent clinically relevant depressive disorder rather than distress symptoms associated with HIV. Furthermore the use of the BDI allows us to access depressive symptoms on a continuum, enabling ascertainment of BDI changes over time and assessment of extreme BDI scores. Over time, any increase in BDI scores associated with detectable CSF HIV RNA, contributes to knowledge of the overall mental health of persons with HIV.

In conclusion, persistent CSF HIV RNA is associated with increased risk of new-onset moderate-to-severe depressive symptoms. Persons with persistent or worsening depression may benefit from CSF testing for HIV RNA, which may help guide HIV and depression treatment. Assessment techniques to determine which patients may benefit from CSF testing may be beneficial. Further research evaluating
the role of immune activation and inflammatory markers will improve our understanding of this association.
Table 4-1. Baseline Characteristics of CHARTER study participants free of DSM-IV major depressive disorder by presence of CSF HIV RNA (≥50 copies/ml)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Total N=223</th>
<th>CSF HIV RNA ≥50 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Detectable n=32 (14.4%)</td>
</tr>
<tr>
<td>Age, mean (SD) yrs</td>
<td>44.8 (7.4)</td>
<td>41.1 (8.3)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>182 (81.6)</td>
<td>154 (80.6)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>88 (39.5 )</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Black</td>
<td>100 (44.8)</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>Hispanic and Other</td>
<td>35 (15.7)</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Education, mean(SD) yrs</td>
<td>12.8 (2.3)</td>
<td>12.8(1.7)</td>
</tr>
<tr>
<td>Log plasma RNA, mean (SD)</td>
<td>2.3 (1.0)</td>
<td>3.8 (1.1)</td>
</tr>
<tr>
<td>Log CSF HIV RNA, mean (SD)</td>
<td>-</td>
<td>2.64 (0.76)</td>
</tr>
<tr>
<td>Current CD4, mean (SD) cells/mm3</td>
<td>477.6</td>
<td>370.3 (270.3)</td>
</tr>
<tr>
<td>CD4 nadir, mean (SD)</td>
<td>145.2</td>
<td>140.7 (145.2)</td>
</tr>
<tr>
<td></td>
<td>(137.2)</td>
<td></td>
</tr>
<tr>
<td>cART Regimen, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>124 (55.6)</td>
<td>26 (81.3)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>79 (35.4)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>PI-NNRTI</td>
<td>11 (4.9)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (4.0)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>CPE 2.0, mean(range)</td>
<td>7.7 (4-14)</td>
<td>7.2 (5-12)</td>
</tr>
<tr>
<td>Adherence, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥95%</td>
<td>192 (86.1)</td>
<td>22 (68.8)</td>
</tr>
<tr>
<td>85-94%</td>
<td>17 (7.6)</td>
<td>2 (6.2)</td>
</tr>
<tr>
<td>&lt;85%</td>
<td>14 (6.3)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Current cART duration, mean(SD), months</td>
<td>18.1 (21.1)</td>
<td>13.6 (20.0)</td>
</tr>
<tr>
<td>Duration of HIV infection, mean (SD), months</td>
<td>139.6</td>
<td>113.0 (66.1)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------</td>
<td>--------------</td>
</tr>
<tr>
<td>Lifetime DSM-IV depression, n(%)</td>
<td>103 (46.2)</td>
<td>20 (62.5)</td>
</tr>
<tr>
<td>Lifetime DSM-IV alcohol use disorder, n(%)</td>
<td>62 (27.8)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Lifetime DSM-IV substance use disorder, n(%)</td>
<td>73 (32.7)</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>BDI score, mean (SD)</td>
<td>12.2 (10.2)</td>
<td>10.5 (9.0)</td>
</tr>
<tr>
<td>Depression, BDI, ≥17, n(%)</td>
<td>86 (34.3)</td>
<td>9 (25.0)</td>
</tr>
<tr>
<td>Cognition, GDS, mean (SD)</td>
<td>0.49 (0.47)</td>
<td>0.37 (0.40)</td>
</tr>
<tr>
<td>HCV positive, n(%)</td>
<td>63 (28.6)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>History of Opportunistic infection, n(%)</td>
<td>38 (44.7)</td>
<td>5 (45.5)</td>
</tr>
</tbody>
</table>

cART: Combination antiretroviral therapy; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; CPE 2.0: CNS penetration effectiveness score 2.0; Adherence assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire; Lifetime depression, substance and alcohol use disorder based on Diagnostic and Statistical Manual of Mental Disorders, IV using the Composite International Diagnostic Interview (CIDI); BDI: Beck Depression Inventory II; GDS: Global Deficit Score.*P < 0.05, **P < 0.01, ***P < 0.001 for difference comparing participants with detectable vs. undetectable CSF HIV RNA.
Table 4-2. Incidence rates and Cumulative Incidence for new-onset moderate-to-severe depressive symptoms based on the Beck Depression Inventory (BDI* score ≥17) by detectable CSF HIV RNA (≥50 copies/ml) and using discrete-time survival models

<table>
<thead>
<tr>
<th></th>
<th>No of subjects (N)</th>
<th>Time at Risk (Person-months)</th>
<th>Incidence rate (IR) per 1,000 person-months</th>
<th>2-year Cumulative Incidence (CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IR (95% CI)</td>
<td>CI (95% CI)</td>
</tr>
<tr>
<td>Entire study cohort</td>
<td>154</td>
<td>2,496</td>
<td>9.6 (6.4, 14.3)</td>
<td>15.6 (10.4, 22.5)</td>
</tr>
<tr>
<td>CSF HIV RNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>141*</td>
<td>2,190</td>
<td>8.2 (5.2, 13.0)</td>
<td>12.8 (7.9, 19.7)</td>
</tr>
<tr>
<td>Detectable</td>
<td>30*</td>
<td>306</td>
<td>19.6 (8.8, 43.6)</td>
<td>20.0 (8.4, 39.1)</td>
</tr>
</tbody>
</table>

*BDI: Beck depression inventory II – depression severity scores: 0-9, minimal; 10-16, mild; 17-29, moderate; 30-63, severe; CSF HIV RNA detectable at ≥50 copies/ml
*Number of subjects per CSF HIV RNA group exceeds total number of subjects because of time-varying nature of detectable CSF HIV RNA status.
Table 4-3. Hazard ratios for the association between detectable CSF HIV RNA (≥50 copies/ml) and new-onset moderate-to-severe depressive symptoms based on the Beck Depression Inventory (BDI* score ≥17) using discrete-time survival models displaying covariates adjusted for in various models

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables adjusted in model</th>
<th>HIV RNA compartment</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unadjusted</td>
<td>CSF†</td>
<td>2.39</td>
<td>(0.98, 5.82)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma†</td>
<td>1.14</td>
<td>(0.78, 1.67)</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>Log plasma HIV RNA/CSF† HIV RNA</td>
<td>CSF</td>
<td>4.70</td>
<td>(1.49, 14.8)</td>
<td>0.008*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>0.81</td>
<td>(0.61, 1.08)</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>Model 2 + Adherence to cART</td>
<td>CSF</td>
<td>4.76</td>
<td>(1.58, 14.3)</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>0.81</td>
<td>(0.61, 1.08)</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>Model 3 + duration of cART</td>
<td>CSF</td>
<td>4.38</td>
<td>(1.48, 13.0)</td>
<td>0.008*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>0.79</td>
<td>(0.60, 1.05)</td>
<td>0.11</td>
</tr>
<tr>
<td>5</td>
<td>Model 4 + Lifetime DSM-IV MDD</td>
<td>CSF</td>
<td>4.74</td>
<td>(1.61, 14.0)</td>
<td>0.005*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>0.82</td>
<td>(0.63, 1.07)</td>
<td>0.15</td>
</tr>
<tr>
<td>6</td>
<td>Model 5 + Sex</td>
<td>CSF</td>
<td>5.08</td>
<td>(1.57, 16.5)</td>
<td>0.007*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>0.86</td>
<td>(0.64, 1.15)</td>
<td>0.31</td>
</tr>
<tr>
<td>7</td>
<td>Model 6 + cART</td>
<td>CSF</td>
<td>6.03</td>
<td>(1.66, 21.9)</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>0.84</td>
<td>(0.62, 1.15)</td>
<td>0.29</td>
</tr>
<tr>
<td>8</td>
<td>Model 7 + Lifetime DSM-IV alcohol and substance use disorder</td>
<td>CSF</td>
<td>6.34</td>
<td>(1.74, 23.3)</td>
<td>0.005*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma</td>
<td>0.82</td>
<td>(0.61, 1.23)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*BDI: Beck depression inventory II – depression severity scores: 0-9, minimal; 10-16, mild; 17-29, moderate; 30-63, severe; †Detectable CSF HIV RNA, ≥50 copies/ml; ‡Log plasma HIV RNA, per 10 RNA copies/ml, categorized plasma RNA: <50, 50-199, 200-999, ≥10,000 copies/ml not associated with new-onset moderate-to-severe depressive symptoms; MDD: Major depressive disorder. DSM IV: Diagnostic and Statistical Manual of Mental Disorders, IV using the Composite International Diagnostic Interview (CIDI DSM-IV).
**Table 4-4.** Longitudinal Effect of Detectable CSF HIV RNA in the Association between detectable CSF HIV RNA (≥50 copies/ml) and Beck Depression Inventory (BDI*) scores over time, using adjusted linear mixed models with random intercept in persons without depression (DSM IV criteria) at baseline

<table>
<thead>
<tr>
<th>Time, months</th>
<th>Coefficient† (95% CI)</th>
<th>p value</th>
<th>Coefficient† (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Ref -</td>
<td>-</td>
<td>Ref -2.99</td>
<td>0.08</td>
</tr>
<tr>
<td>6</td>
<td>-1.67 (-3.11, -0.23)</td>
<td>0.02*</td>
<td>3.72 (0.32, 7.13)</td>
<td>0.03*</td>
</tr>
<tr>
<td>12</td>
<td>-2.72 (-4.41, -1.03)</td>
<td>0.002*</td>
<td>3.72 (-0.03, 7.46)</td>
<td>0.05*</td>
</tr>
<tr>
<td>18</td>
<td>-3.54 (-5.65, -1.42)</td>
<td>0.001*</td>
<td>4.56 (0.71, 8.41)</td>
<td>0.02*</td>
</tr>
<tr>
<td>24</td>
<td>-3.74 (-6.28, -1.20)</td>
<td>0.004*</td>
<td>3.02 (-1.19, 7.22)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*BDI: Beck depression inventory II; depression severity scores: 0-9, minimal; 10-16, mild; 17-29, moderate; 30-63, severe.
† Coefficient represents the longitudinal change in BDI scores from baseline with reference to persons without detectable CSF HIV RNA in multivariate linear mixed models adjusted for log plasma HIV RNA, race, age, sex, education, nadir and current CD4 counts, CNS Penetration Effectiveness 2.0 score (CPE 2.0), lifetime DSM-IV depression and depression at prior visit, lifetime DSM-IV alcohol and substance use disorder, years infected with HIV, cognitive impairment (global deficit score- GDS), and prior diagnosis of HCV infection.
Table 4-5. Cross-sectional Effect of Detectable CSF HIV RNA over time for the Association between detectable CSF HIV RNA (≥50 copies/ml) and Beck Depression Inventory (BDI*) scores over time using adjusted linear mixed models with random intercept in persons without depression (DSM IV criteria) at baseline

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unadjusted model estimates</th>
<th>Adjusted† model estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>CSF HIV RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Detectable</td>
<td>0.51</td>
<td>(-1.16, 2.19)</td>
</tr>
<tr>
<td>Log Plasma HIV RNA (per 10 RNA copies/ml)</td>
<td>0.53</td>
<td>(-0.29, 1.35)</td>
</tr>
</tbody>
</table>

*BDI: Beck depression inventory II; depression severity scores: 0-9, minimal; 10-16, mild; 17-29, moderate; 30-63, severe.
† Coefficient represents the longitudinal change in BDI scores from baseline with reference to persons without detectable CSF HIV RNA in multivariate linear mixed models adjusted for log plasma HIV RNA, race, age, sex, education, nadir and current CD4 counts, CNS Penetration Effectiveness 2.0 score (CPE 2.0), lifetime DSM-IV depression and depression at prior visit, lifetime DSM-IV alcohol and substance use disorder, years infected with HIV, cognitive impairment (global deficit score- GDS), and prior diagnosis of HCV infection.
Figure 4-1. Incidence rates (IR) for new-onset moderate-to-severe depressive symptoms assessed using the Beck Depression Inventory (BDI* score ≥17) by detectable CSF HIV RNA (≥50 copies/ml) using discrete-time survival models.

Incidence rates expressed per 1,000 person months. Adjusted HR=4.76, 95% CI: 1.58, 14.3; P=0.006, adjusted for plasma HIV RNA and treatment adherence. CSF HIV RNA detectable at a threshold of ≥50 copies/ml. *Depression assessed by Beck depression inventory II (BDI); depression severity scores: 0-9, minimal; 10-16, mild; 17-29, moderate; 30-63, severe.
**Figure 4-2.** Longitudinal effect of detectable CSF HIV RNA (≥50 copies/ml) on Beck Depression Inventory (BDI*) scores using adjusted† linear mixed models with random intercept in persons without depression (DSM IV criteria) at study entry

Change in depression (BDI) scores represents the longitudinal change in BDI scores from baseline with reference to persons without detectable CSF HIV RNA. *P<0.05.

*Depression assessed by Beck depression inventory II (BDI); depression severity scores: 0-9, minimal; 10-16, mild; 17-29, moderate; 30-63, severe.

†Multivariate linear mixed model adjusted for log plasma HIV RNA, race, age, sex, education, nadir and current CD4 counts, CNS Penetration Effectiveness 2.0 score (CPE 2.0), lifetime depression diagnosis, depression at prior study visit, years infected with HIV, cognitive impairment (global deficit score- GDS), and prior diagnosis of HCV infection.
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CHAPTER 5

THE BURDEN OF CSF VIRAL ESCAPE IN PERSONS WITH HIV: INCREASED RISK ASSOCIATED WITH MAJOR DEPRESSIVE DISORDER
ABSTRACT

**Background:** Major depressive disorder (MDD) is associated with poor virologic outcomes and faster HIV progression. Although persistent cerebrospinal fluid (CSF) HIV RNA is associated with MDD, it is unknown whether MDD is associated with detectable CSF virus with undetectable plasma virus in persons taking antiretroviral drugs (CSF viral escape).

**Methods:** Using the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) prospective cohort, a six center, US-based study, we fit logistic regression models to examine the association between DSM-IV MDD and CSF viral escape among 803 participants who completed CSF examination at study entry. Longitudinal analyses were performed among 212 participants without CSF viral escape at study entry who received at least 3 CSF examinations over 2,736 person-months, a total of 668 observations.

**Results:** The overall prevalence of CSF viral escape at study entry was 17.6% (n=141). Among persons with MDD, the prevalence of CSF viral escape was 25.7%, compared to those without MDD, 16.3%, \( P=0.016 \). The population 18-month cumulative incidence of CSF viral escape was 15.1%, increasing to 26.1% in persons with MDD. The incidence of CSF viral escape was 3-fold higher in persons with MDD (20.0 per 1,000 persons-months; 95% Confidence Interval (CI): 9.0-44.5) relative to persons without MDD (10.7 per 1,000 person-months; 95% CI: 7.3-15.7); adjusted hazard ratio (HR)=3.01; 95% CI: 1.03-8.78, \( P=0.043 \).

**Discussion:** MDD is associated with increased risk for CSF viral escape. Ongoing CSF viral replication may occur in more persons than previously estimated. Careful
evaluation and treatment of depression may improve HIV control. Additional research is needed to continue to improve our understanding of mechanisms that may be responsible for the relationship between depression and HIV viral replication.
BACKGROUND

Major depressive disorder (MDD) in HIV is associated with a more rapid decline in CD4 cell count and progression to AIDS (Ickovics et al., 2001; Mayne, Vittinghoff, Chesney, Barrett, & Coates, 1996; Page-Shafer, Delorenze, Satariano, & Winkelstein, 1996). MDD is associated with an increased risk of acquiring and spreading HIV, reduction in treatment adherence, and greater mortality (Hutton, Lyketsos, Zenilman, Thompson, & Erbelding, 2004; Kacanek et al., 2010). Substance use and addiction, high-risk sexual behavior and access to care are some of the mechanisms that may be involved in the association between MDD and the acquisition or progression of HIV (Chander, Himelhoch, & Moore, 2006; Hutton et al., 2004; Kacanek et al., 2010). HIV progression has likewise been shown to be associated with increased risk of depression (Lyketsos et al., 1996).

Depression is associated with immune suppression (impaired innate and adaptive immune responses), and immune activation (up-regulation of pro-inflammatory cytokines) (Blume, Douglas, & Evans, 2011; Evans et al., 2002; Pike & Irwin, 2006; Raison, Capuron, & Miller, 2006). Cerebrospinal fluid (CSF) viral escape defined as detectable CSF HIV RNA (>50 copies/mL) in the presence of clinically undetectable plasma levels (<50 copies/mL) or CSF HIV RNA concentration ≥1 log greater than the plasma HIV RNA concentration (Canestri et al., 2010; Eden et al., 2010; Peluso et al., 2012), has been reported in persons on combination antiretroviral therapy (cART) with undetectable plasma RNA (Eden et al., 2010; Peluso et al., 2012).
Antiretroviral drug concentrations in CSF are almost always lower than in blood, often by several orders of magnitude (Eisfeld, Reichelt, Evers, & Husstedt, 2013). This implies that the barrier to loss of viral suppression in CSF is easier to breach than in other tissues. Even when plasma HIV RNA concentrations have been effectively suppressed by cART to undetectable levels, immune activation of the central nervous system (CNS) may persist (Eden et al., 2007). Persistent immune activation of the CNS by low-level viremia may play a role in the development of depression (Raison et al., 2010). However, it is not clear if depression may increase the risk for subsequent CSF viral escape.

In this study we examined whether MDD is associated with CSF viral escape using cross-sectional and prospective data from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort.

METHODS

Study design and Participants

CHARTER is a six-center, US-based prospective, observational study initiated in 2004 and designed to comprehensively assess a demographically representative US population who are HIV-seropositive in clinical care (Heaton et al., 2010). The goal of CHARTER is to evaluate the changing presentation of HIV neurological complications in the context of cART. There were no general exclusion criteria in CHARTER except the inability to consent to participation in study assessments. Study sites include Johns Hopkins University, Baltimore, MD; Icahn School of Medicine at Mt. Sinai, New York, NY; University of California, San Diego, CA;
University of Texas, Galveston, TX; University of Washington, Seattle, WA; and Washington University, St. Louis, MO. The study was approved by the Institutional Review Board (IRB) or Western IRB for each study site and each participant provided written informed consent.

At study entry, 1561 CHARTER participants, of whom 1,053 were currently on cART, underwent extensive evaluation including HIV and treatment history verified by medical records, physical examination, neuropsychiatric evaluation, neuropsychological testing lumbar puncture, and venipuncture. Thereafter 674 participants who consented to biannual evaluations were selected to undergo follow-up visits every 6-months as part of the longitudinal study component.

For these analyses, we utilized data from the baseline assessment (cross-sectional analysis) and the cohort of participants enrolled between 2004 and 2007 and followed through 2009 (longitudinal analysis) (Heaton et al., 2010). Participants were included in the cross-sectional analysis if they completed CSF HIV RNA testing at study entry (n=803), in addition to plasma HIV RNA testing. Reasons for not completing the lumbar puncture include unsuccessful procedures and participant unwillingness. For the longitudinal data analysis, participants were included if they had completed at least three study visits where lumbar puncture was successfully performed (n=212). We excluded four participants with missing current MDD status in cross-sectional analyses. In longitudinal analyses, we aimed to assess incidence of CSF viral escape, so we excluded the 42 participants with CSF viral escape at baseline. Socio-demographic and clinical characteristics of participants excluded from the analyses were not significantly different from those
retained in either cross-sectional or longitudinal analyses. In both cross-sectional and longitudinal analysis, our sample size allowed for detecting a difference in prevalence or incidence of CSF viral escape by MDD status with at least 80% power at Type I error of 0.05.

**Measures**

The principal outcome variable was CSF viral escape defined as detectable CSF HIV RNA (>50 copies/mL) in the presence of undetectable plasma HIV RNA (<50 copies/mL) or CSF HIV RNA concentration ≥1 log greater than the plasma HIV RNA concentration (Canestri et al., 2010; Eden et al., 2010; Peluso et al., 2012). CSF and plasma HIV RNA concentrations were determined by commercial ultrasensitive reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostic Systems, Indianapolis, Indiana). CSF viral escape was assessed at each study visit.

The main exposure of interest was a diagnosis of current DSM-IV MDD (within the past 30 days) measured at each study visit based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria assessed using the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) (Kessler & Ustun, 2004). We incorporated both fixed and time-varying covariates in our analysis. The fixed covariates were patient demographics (age, sex, race, and years of education), self-reported duration of HIV seropositivity, self-reported nadir CD4+ T-cell, lifetime history of DSM-IV MDD, lifetime history of alcohol and substance use disorder assessed by the CIDI, and HCV seropositivity. Time-varying covariates assessed at each study visit include DSM-IV MDD, selective serotonin re-
uptake inhibitor (SSRI) use, current CD4+ T-cell count, cognitive impairment
assessed by the Global Deficit Score (GDS) (Carey et al., 2004), which summarizes
overall functioning across seven constructs from the standardized comprehensive
neurocognitive assessment, current cART regimen (protease inhibitor vs. non-
nucleoside reverse transcriptase inhibitor based regimen) and duration of cART
regimen, CNS penetration effectiveness (CPE 2.0) score of current cART which is an
estimate of the extent to which antiretroviral drugs affect the CNS (Letendre et al.,
2008; Letendre, Ellis, Ances, & McCutchan, 2010), and medication adherence
assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire (Chesney
et al., 2000).

Statistical analysis

We examined study population characteristics using summary statistics. To assess
the association between MDD and CSF virologic escape in cross-sectional analysis,
we fit univariate and multivariate logistic regression models. To examine the effect
of MDD on CSF viral escape in longitudinal data analyses, we fit discrete-time
survival models to estimate hazard odds ratios of CSF viral escape (Willett & Singer,
1993).

We examined interactions between current/lifetime MDD and cART regimen
use because protease inhibitor-based cART has been associated with decreased
depression scores (Low-Beer et al., 2000). We also examined interactions between
adherence to cART with current cART regimen and current MDD. To examine the
joint hypothesis that coefficients of the interactions were zero, we performed a
Wald test. We performed a sensitivity analysis and model checks. Author ERH performed the Statistical analysis using *Stata Statistical Software: Release 12.* (College Station, TX: StataCorp LP).

**RESULTS**

*Cross-sectional evaluation*

A total of 803 participants were included in our cross-sectional evaluation. The population mean age was 43.9 years, predominantly male (80.6%), with 46.2% Blacks (*Table 5-1*). At study entry, MDD was prevalent in 109 (13.6%) of the participants. The overall prevalence of CSF viral escape at study entry was 17.6%. Among persons with MDD, the prevalence of CSF viral escape was 25.7%, compared to 16.3% without MDD (*P*=0.016, *Table 5-1, Figure 5-1*).

In univariate logistic regression models, the odds of CSF viral escape in participants with current MDD was 78% higher than in participants without MDD (unadjusted OR=1.78; 95% CI: 1.11-2.86, *P*=0.018) (*Table 5-2*). After adjusting for adherence to cART, nadir and current CD4+ T-cell counts, CPE 2.0, use of protease inhibitor-based cART regimen, duration of HIV seropositivity, lifetime history of MDD, lifetime substance and alcohol use disorder, age, sex, and education, persons with current MDD at baseline had more than twice the odds of CSF viral escape compared to persons without current MDD (adjusted OR=2.10; 95% CI: 1.15-3.84, *P*=0.016) (*Table 5-2*). Unlike current MDD, a lifetime history of MDD was not associated with CSF viral escape.
Other characteristics found to be associated with CSF viral escape included individuals of Black and Hispanic race relative to White participants (adjusted OR=1.74, 95% CI=1.06-2.87, \( P=0.029 \), and adjusted OR=2.20, 95% CI=1.15-4.16, \( P=0.016 \) for Blacks and Hispanics, respectively (Table 5-2)). In addition, less than 85% adherence to cART was associated with a 3-fold increase in odds of CSF viral escape compared to those with \( \geq 95\% \) adherence.

Covariates associated with decreased odds of CSF viral escape in the multivariate analysis include current CD4 cell counts \( \geq 200 \) cells/mm\(^3\), increasing CPE score and a history of lifetime substance use disorder. A history of an opportunistic infection and use of protease inhibitor-based cART regimen were associated with greater odds of CSF viral escape. There were no significant interactions between current cART regimen with current or lifetime MDD or between adherence to cART with current cART regimen, race or current MDD.

**Longitudinal evaluation**

The 212 participants without CSF viral escape at baseline who were included in the longitudinal analysis contributed a total of 2,736 person-months of follow-up. We present our final adjusted discrete-time proportional hazards model selected after comparing several nested models in Table 5-3. The overall incidence of new CSF viral escape was 11.7 per 1,000 person-months (95% CI: 8.3-16.5 per 1,000 person-months), with an 18-month cumulative incidence of 15.1%. The incidence of CSF viral escape was higher in persons with MDD (20.0 per 1,000 persons-months; 95%
CI: 9.0-44.5) compared to persons without MDD (10.7 per 1,000 person-months; 95% CI: 7.3-15.7) (Figure 5-2).

Although the incidence of CSF viral escape was higher in persons with MDD, there was no difference in plasma viral load comparing persons with MDD to those without MDD. Persons with MDD had a 3-fold increased risk of new CSF viral escape (adjusted HR=3.01; 95% CI: 1.03-8.78, P=0.043), after adjustment for sociodemographic characteristics, cART regimen, adherence, CPE 2.0, current CD4 cell count, lifetime alcohol or substance use disorder, duration of HIV infection, treatment duration and with selective serotonin re-uptake inhibitors (SSRI) use. (Final Model, Table 5-3). Our findings for the longitudinal evaluation assessing the association between MDD and CSF viral escape were consistent with those observed in the cross-sectional analyses.

The 18-month cumulative incidence of CSF viral escape was higher in persons with MDD (26.1%), compared to 13.8% in persons without MDD. There were no significant interactions between current cART regimen with current or lifetime MDD or between adherence to cART with current cART regimen and current MDD.

DISCUSSION

MDD and CSF viral escape

In this report, we found that major depressive disorder (MDD) in persons with HIV is associated with a higher prevalence and incidence of CSF viral escape. MDD is also associated with a 3-fold increased risk of new CSF viral escape in persons followed
over time with an average of three CSF examinations. Our findings suggest that MDD is associated with increased viral replication in CSF compared to plasma. These findings contribute to our understanding of the associations between HIV and MDD, and may offer an explanation for treatment escape occurring in the CNS.

The overall incidence rates and 18-month cumulative incidence of CSF viral escape in this study population of persons with established HIV disease on long-term cART suggests that persistent CSF viral replication may occur more frequently than previously thought. Persons with MDD may experience even higher levels of persistent CSF viral replication. The 17.6% prevalence of CSF viral escape in our population is higher than earlier reports suggesting 10% prevalence (Eden et al., 2010). Previous evaluations of CSF viral escape have taken place in relatively small populations (Cusini et al., 2013; Eden et al., 2007; Eden et al., 2010; Peluso et al., 2012). The design and size of CHARTER provide a more representative sample of the general HIV patient population and hence the first representative reports of the burden of CSF viral escape.

The association between MDD and HIV may represent a bidirectional relationship. HIV may increase risk for MDD, and MDD in turn may result in progression of HIV. Factors that potentially could bidirectionally impact the HIV-MDD association include non-adherence to cART, high-risk HIV behavior in persons with depression, CNS penetration of cART, residual CNS viral replication, genetic differences, a history of prior depressive illness and access to care (Hutton et al., 2004; Kacanek et al., 2010; S. L. Letendre et al., 2010; Samson et al., 1996; Tedaldi, Absalon, Thomas, Shlay, & van den Berg-Wolf, 2008). In this analysis, we observed
that <85% adherence to cART is associated with increased odds of CSF viral escape. Persons with depression are more likely to engage in high-risk HIV behavior resulting in re-infection and poor viral control. However, even taking into account measures of adherence, depression had a positive association with viral escape both in our cross-sectional and longitudinal assessments.

The bi-directional nature of the HIV-MDD association may also be due to immune-mediated activation of various cellular pathways. One possible mechanism may be through the activation of the enzyme indolamine-2,3,-dioxygenase (IDO) pathway (Raison et al., 2006; Raison et al., 2010). When the innate and adaptive immune systems are activated by replicating HIV RNA, circulating inflammatory cytokines may activate IDO (Boasso et al., 2007; Catalfamo et al., 2011). The catabolic enzyme IDO, which breaks down L-tryptophan to L-kynurenine, may result in depleted stores of L-tryptophan, a precursor of serotonin. Decreased serotonin production, transmission or increased uptake at the neuromuscular junction is implicated in the pathogenesis and treatment of mood disorders including MDD (Dursun & Reveley, 1995). In persons with HIV, dysregulated serotonergic transmission measured by a serotonin-specific transporter radioligand for positron emission tomography may be associated with depression (Hammoud et al., 2010).

The immunosuppressive effect of IDO may be exerted through depletion of L-tryptophan and interference with T-cell regulation potentially resulting in functional impairment and depletion of CD4 T-cells (Boasso et al., 2007; Mellor et al., 2003). In addition to causing depression by activating the tryptophan-catabolizing and immunosuppressive enzyme IDO through inflammatory mediators,
the presence of CSF HIV RNA may also lead to poor viral control and increased HIV replication.

Persistent CSF viral replication may result from variability in the extent of CNS penetration of HIV drugs (Gisolf et al., 2000; Yilmaz et al., 2008), and is associated with increased intrathecal immune activation, progressive neurologic deficits, depression and development of resistant viral strains (Eden et al., 2007; Peluso et al., 2012; Smit et al., 2004). This may suggest a need for CSF testing in persons with HIV who have progression of neurologic disease or worsening depression.

**Additional findings**

Some consideration must be given to our observation that the use of protease inhibitor-based cART regimen is associated with increased odds of CSF viral escape. Commonly used protease inhibitors have good CNS penetration, lopinavir/ritonavir (CPE score 3.0) and atazanavir/ritonavir (CPE score 2.0) (Letendre et al., 2010), making it unlikely that the observed association is a direct effect of the medications. Yet, the observed association between protease inhibitor-based cART regimen and increased odds of CSF viral escape may represent confounding by indication. For example, because protease inhibitors have been associated with decreased depression scores (Low-Beer et al., 2000), they may be favored in persons who have ongoing depression or a lifetime history of depression. In addition, because low adherence among persons on protease inhibitors are less likely to increase the risk of drug resistance compared to non-nucleoside reverse transcriptase inhibitor
(NNRTI) regimen (Hsieh et al., 2013), protease inhibitors may be favored in persons who are more likely to be non-adherent to treatment. However, we did not observe significant interactions between protease inhibitor-based cART or adherence to cART with MDD and CSF viral escape. Further investigation into this observation is warranted to tease out any potential residual confounding that may explain the increased CSF viral escape associated with protease inhibitor use.

As expected, improved immune function evidenced by increasing CD4 cell counts was associated with decreased odds of CSF viral escape. Similarly cART regimen with better CNS penetration was associated with decreased odds of CSF viral escape. Any increase in the CPE of cART regimen was associated with 17% decreased odds of CSF viral escape. In balancing the benefits and extent of CNS penetrance to potential drug toxicity, it may be beneficial to examine if there is an upper limit to the benefits of CNS penetration of cART.

Biological mechanisms such as racial differences in genetic expression of the human chemokine receptor 5 (CCR5) which confers resistance to HIV-1 infection among Whites (Samson et al., 1996), as well as the many issues related to racial disparities in care (Tedaldi et al., 2008), are possible explanations for our findings that Blacks and Hispanics with other ethnic minority races showed greater odds of CSF viral escape relative to Whites. We did not observe interactions between race and adherence.

The selective serotonin reuptake inhibitor (SSRI) class of antidepressant is associated with lower HIV replication (Benton et al., 2010; S. L. Letendre et al., 2007). SSRIs fulfill the conditions as a confounder of the MDD-CSF viral escape
association, being associated with both MDD and CSF viral escape, but not within the causal pathway. In longitudinal analyses we did not observe an association between SSRIs use and CSF viral escape. As expected of a negative confounder however, accounting for SSRI use in our analyses increased the observed measure of association from an adjusted HR of 2.81 to 3.01 (Table 5-3: Model 4 and Final). This suggests that although we did not observe an association between SSRI use and CSF viral escape, SSRIs may still be of benefit in some patients, providing CNS “antiviral” effects previously reported (Letendre et al., 2007).

Limitations and Strengths

There remain some limitations to consider when interpreting our findings. First, we did not include information for all depression treatment received because the information was not available. However we accounted for DSM-IV MDD measured at each study visit in our longitudinal analysis, and also accounted for a history of lifetime depression. This approach may indirectly adjust for depression treatment received. Second, we were not able to assess whether viral replication mediated the association between MDD and CSF viral escape, which will need to be examined in future investigations. Third, we did not evaluate the effect of current substance and alcohol use disorder because a diagnosis of current substance or alcohol use disorder was relatively infrequent, 0.9% and 0.8% of the population, respectively. However we were able to account for lifetime substance and alcohol use disorder.

In addition to the relatively large CHARTER sample and prospective design, bi-annual CSF testing for participants in the longitudinal arm of the CHARTER study
was a unique strength of the study. The main exposure, DSM-IV MDD, and outcome, CSF viral escape, were measured at each study visit. In addition, we were able to complete both cross-sectional and longitudinal analyses of the hypothesized associations. Our methodologic approach was able to incorporate the longitudinal assessment of MDD and the time-varying nature CSF viral escape, thereby reducing potential for biased estimates of the association. To our knowledge, prior reports have not evaluated the incidence and cumulative incidence of CSF viral escape.

**Conclusion**

In summary, MDD is associated with increased risk for CSF viral escape. Ongoing CSF viral replication may occur in more persons than previously estimated. Our findings may help identify future directions for MDD treatment and HIV management. Careful evaluation and treatment of depression may improve HIV control. Additional research is needed to continue to improve our understanding of mechanisms that may be responsible for the relationship between depression and HIV viral replication.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total  (N=803)</th>
<th>Major depressive disorder</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Depressed n=109 (13.6%)</td>
<td>Not depressed n=694 (86.4%)</td>
</tr>
<tr>
<td>CSF Viral Escape, n (%)</td>
<td>141 (17.6)</td>
<td>28 (25.7)</td>
<td>113 (16.3)</td>
</tr>
<tr>
<td>Age, mean (SD) yrs</td>
<td>43.9 (7.9)</td>
<td>44.0 (8.1)</td>
<td>43.9 (7.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>647 (80.6)</td>
<td>87 (79.9)</td>
<td>560 (80.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>328 (40.9)</td>
<td>57 (52.3)</td>
<td>271 (39.1)</td>
</tr>
<tr>
<td>Black</td>
<td>371 (46.2)</td>
<td>34 (31.2)</td>
<td>337 (48.6)</td>
</tr>
<tr>
<td>Hispanic and Other</td>
<td>104 (13.0)</td>
<td>18 (16.5)</td>
<td>86 (12.4)</td>
</tr>
<tr>
<td>Education, mean (SD) yrs</td>
<td>12.6 (2.6)</td>
<td>12.7 (2.9)</td>
<td>12.5 (2.5)</td>
</tr>
<tr>
<td>Log plasma RNA, mean (SD)</td>
<td>1.62 (1.61)</td>
<td>1.64 (1.69)</td>
<td>1.62 (1.60)</td>
</tr>
<tr>
<td>Log CSF HIV RNA, mean (SD)</td>
<td>0.58 (1.06)</td>
<td>0.74 (1.27)</td>
<td>0.56 (1.02)</td>
</tr>
<tr>
<td>Current CD4, mean (SD) cells/mm3</td>
<td>445.3 (281.6)</td>
<td>499.6 (318.2)</td>
<td>436.8 (274.7)</td>
</tr>
<tr>
<td>CD4 nadir, mean (SD)</td>
<td>149.3 (143.9)</td>
<td>163.1 (137.5)</td>
<td>147.1 (144.9)</td>
</tr>
<tr>
<td>cART Regimen, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI-based regimen</td>
<td>492 (61.3)</td>
<td>72 (66.1)</td>
<td>420 (60.5)</td>
</tr>
<tr>
<td>Non-PI based</td>
<td>311 (38.7)</td>
<td>37 (33.9)</td>
<td>274 (39.5)</td>
</tr>
<tr>
<td>cART Regimen, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>453 (56.4)</td>
<td>67 (61.5)</td>
<td>386 (55.6)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>286 (35.6)</td>
<td>35 (32.1)</td>
<td>251 (36.2)</td>
</tr>
<tr>
<td>PI-NNRTI</td>
<td>39 (4.9)</td>
<td>5 (4.6)</td>
<td>34 (4.9)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (3.1)</td>
<td>2 (1.8)</td>
<td>23 (3.3)</td>
</tr>
<tr>
<td>CPE 2.0, median (range)</td>
<td>7.0 (3-15)</td>
<td>7.0 (4-12)</td>
<td>7.0 (3-15)</td>
</tr>
<tr>
<td>Adherence, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥95%</td>
<td>694 (87.0)</td>
<td>93 (86.1)</td>
<td>601 (87.0)</td>
</tr>
<tr>
<td>85-94%</td>
<td>36 (4.5)</td>
<td>4 (3.7)</td>
<td>32 (4.6)</td>
</tr>
<tr>
<td>&lt;85%</td>
<td>68 (8.5)</td>
<td>11 (10.2)</td>
<td>57 (8.3)</td>
</tr>
<tr>
<td>HIV Duration, mean (SD), yrs.</td>
<td>10.8 (6.2)</td>
<td>10.9 (6.2)</td>
<td>10.7 (6.2)</td>
</tr>
<tr>
<td>Lifetime DSM-IV MDD, n (%)</td>
<td>403 (50.2)</td>
<td>109 (100.0)</td>
<td>294 (42.4)</td>
</tr>
<tr>
<td>Lifetime alcohol abuse, n (%)</td>
<td>223 (27.8)</td>
<td>26 (23.9)</td>
<td>197 (28.4)</td>
</tr>
<tr>
<td>Lifetime substance abuse, n(%)</td>
<td>276 (34.4)</td>
<td>34 (31.2)</td>
<td>242 (34.9)</td>
</tr>
</tbody>
</table>

Table 5-1. Baseline Characteristics of CHARTER study participants by major depressive disorder (DSM-IV MDD) at study entry, N=803
<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition, GDS, median</td>
<td>0.42</td>
<td>(0.16-0.84)</td>
<td>0.42</td>
<td>(0.16-1.42)</td>
<td>0.42</td>
</tr>
<tr>
<td>(IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior HCV infection, n(%)</td>
<td>217</td>
<td>(27.5)</td>
<td>23</td>
<td>(21.5)</td>
<td>194</td>
</tr>
<tr>
<td>Prior Opportunistic</td>
<td>118</td>
<td>(14.7)</td>
<td>7</td>
<td>(6.4)</td>
<td>111</td>
</tr>
<tr>
<td>infection, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

cART: Combination antiretroviral therapy; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; CPE 2.0: CNS penetration effectiveness score 2.0; Adherence assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire; Lifetime depression assessed by DSM-IV using the Composite International Diagnostic Interview (CIDI); Lifetime alcohol and substance use disorder assessed by DSM-IV CIDI; GDS: Global Deficit Score; MDD: Major depressive disorder; SD: standard deviation; IQR: inter-quartile range; P-value assessed by chi-square for categorical variables and t-test for continuous variables; *p<0.05
Table 5-2. Odds ratios (OR) for the cross-sectional association between a current diagnosis of major depressive disorder (DSM-IV MDD) and CSF viral escape among CHARTER study participants at baseline using logistic regression models, N=803

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unadjusted model estimates</th>
<th>Adjusted† model estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current MDD diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>1.78 (1.11-2.86)</td>
<td>2.10 (1.15-3.84)</td>
</tr>
<tr>
<td>Sex; Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Male</td>
<td>1.27 (0.82-1.98)</td>
<td>1.08 (0.63-1.84)</td>
</tr>
<tr>
<td>Age, mean (SD) yrs</td>
<td>0.98 (0.96-1.00)</td>
<td>Ref (0.97-1.03)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Black</td>
<td>1.97 (1.30-2.99)</td>
<td>1.74 (1.06-2.87)</td>
</tr>
<tr>
<td>Hispanic/Other</td>
<td>2.22 (1.26-3.91)</td>
<td>2.20 (1.16-4.16)</td>
</tr>
<tr>
<td>Education, (yrs)</td>
<td>0.94 (0.87-1.01)</td>
<td>0.97 (0.89-1.07)</td>
</tr>
<tr>
<td>Current CD4, cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>200-499</td>
<td>0.54 (0.34-0.84)</td>
<td>0.51 (0.29-0.88)</td>
</tr>
<tr>
<td>≥500</td>
<td>0.36 (0.22-0.59)</td>
<td>0.33 (0.17-0.64)</td>
</tr>
<tr>
<td>CD4 nadir, cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>100-199</td>
<td>0.78 (0.49-1.24)</td>
<td>1.26 (0.72-2.19)</td>
</tr>
<tr>
<td>≥200</td>
<td>0.85 (0.55-1.31)</td>
<td>1.89 (1.06-3.36)</td>
</tr>
<tr>
<td>PI-based cART regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2.07 (1.38-3.12)</td>
<td>1.58 (1.01-2.52)</td>
</tr>
<tr>
<td>CPE score, (per 1 pt.)</td>
<td>0.83 (0.74-0.94)</td>
<td>0.83 (0.73-0.94)</td>
</tr>
<tr>
<td>CPE2.0 score,*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>7-8</td>
<td>0.48 (0.32-0.72)</td>
<td>0.56 (0.35-0.90)</td>
</tr>
<tr>
<td>≥9</td>
<td>0.62 (0.38-1.02)</td>
<td>0.62 (0.35-1.10)</td>
</tr>
<tr>
<td>Adherence,%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of HIV infection, years</td>
<td>Ref</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----</td>
<td>----------</td>
</tr>
<tr>
<td>≥95</td>
<td>1.35</td>
<td>(0.58-3.17)</td>
</tr>
<tr>
<td>85-95</td>
<td>3.47</td>
<td>(2.04-5.91)</td>
</tr>
<tr>
<td>&lt;85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.43</td>
<td>(0.82-2.46)</td>
</tr>
<tr>
<td>5-10</td>
<td>1.31</td>
<td>(0.81-2.12)</td>
</tr>
<tr>
<td>&gt;10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime DSM-IV MDD</td>
<td>1.16</td>
<td>(0.8-1.67)</td>
</tr>
<tr>
<td>Lifetime DSM-IV alcohol use disorder</td>
<td>0.78</td>
<td>(0.50-1.16)</td>
</tr>
<tr>
<td>Lifetime DSM-IV substance use disorder</td>
<td>0.50</td>
<td>(0.33-0.77)</td>
</tr>
<tr>
<td>Cognition, GDS (continuous)</td>
<td>0.81</td>
<td>(0.58-1.14)</td>
</tr>
<tr>
<td>Prior HCV infection</td>
<td>0.69</td>
<td>(0.44-1.08)</td>
</tr>
<tr>
<td>Prior Opportunistic infection</td>
<td>1.57</td>
<td>(0.98-2.52)</td>
</tr>
</tbody>
</table>

MDD: major depressive disorder; OR: Odds ratio; †Adjusted Odds Ratio: adjusted for nadir and current CD4 count, CPE2.0 (CNS penetration effectiveness 2.0), current duration of cART, cART adherence (AIDS Clinical Trials Group 4-Day Adherence Questionnaire), age, sex, race, education, duration of HIV infection, lifetime depression diagnosis by DSM-IV criteria, lifetime alcohol and substance abuse by DSM-IV criteria, cognitive impairment (global deficit score, GDS), prior diagnosis of HCV infection, prior history of opportunistic infection, cART: combination antiretroviral therapy.

*Separate multivariable model fit for categorized CPE2.0 score.
Table 5-3. Hazard ratios for the *longitudinal* association between DSM-IV major depressive disorder and new-onset CSF viral escape using discrete-time survival models in persons free of CSF viral escape at baseline, N=212

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables adjusted in model</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unadjusted</td>
<td>1.75</td>
<td>(0.72, 4.22)</td>
<td>0.214</td>
</tr>
<tr>
<td>2</td>
<td>Model 1 + <em>Demographics</em> (Race, Sex, Age)</td>
<td>2.27</td>
<td>(0.93, 5.56)</td>
<td>0.072</td>
</tr>
<tr>
<td>3</td>
<td>Model 2 + <em>Treatment</em> (CD4, CPE 2.0, cART, adherence)</td>
<td>2.71</td>
<td>(1.02, 7.21)</td>
<td>0.046*</td>
</tr>
<tr>
<td>4</td>
<td>Model 3 + Duration of <em>HIV infection, treatment duration, substance and alcohol use disorder</em></td>
<td>2.81</td>
<td>(1.02, 7.77)</td>
<td>0.046*</td>
</tr>
<tr>
<td><strong>Final</strong></td>
<td>Model 4 + <em>SSRI use</em></td>
<td>3.01</td>
<td>(1.03, 8.78)</td>
<td>0.043*</td>
</tr>
</tbody>
</table>

CPE2.0: CNS penetration effectiveness score 2.0; adherence by AIDS Clinical Trials Group 4-Day Adherence Questionnaire; cART: combination antiretroviral therapy; lifetime alcohol and substance use disorder based on Diagnostic and Statistical Manual of Mental Disorders, IV using the Composite International Diagnostic Interview (CIDI DSM-IV); cART: combination antiretroviral therapy; SSRI: selective serotonin reuptake inhibitor.
Figure 5-1. Prevalence of CSF viral failure by DSM-IV major depressive disorder at study entry among participants in the CHARTER study, N=803

Adjusted Odds ratio=2.10; 95% CI: 1.15—3.84, $P=0.016$, adjusted for adherence to cART, nadir and current CD4+ T-cell counts, CPE 2.0, use of protease inhibitor-based cART regimen, duration of HIV seropositivity, lifetime history of MDD, lifetime substance and alcohol use disorder, age, sex, and education.
**Figure 5-2.** Cumulative incidence rates of new-onset CSF viral escape (*panel A*) and plasma viral load trends (*panel B*) by DSM-IV major depressive disorder status over 18-months follow-up in the CHARTER study, N=212

Adjusted hazard ratio=3.01; 95% CI: 1.03—8.78, *p*=0.043, adjusted for adherence to cART, protease inhibitor-based cART regimen, current CD4 cell count, lifetime alcohol and substance use disorder, HIV and treatment duration, SSRI use, age, sex and race.
References

doi:10.1097/PSY.0b013e3181f883ce


doi:10.1086/650538; 10.1086/650538


doi:10.1080/13803390490510031


doi:10.1080/0954012050042891

Syndromes (1999), 62(1), 28-35. doi:10.1097/QAI.0b013e318274e2b0; 10.1097/QAI.0b013e318274e2b0


bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature, 382*(6593), 722-725. doi:10.1038/382722a0


CHAPTER 6

DIAGNOSTIC PROPERTIES OF THE CSF RISK SCORE AND ITS ASSOCIATION WITH CSF VIRAL ESCAPE
ABSTRACT

**Background:** Residual viral replication can occur in the cerebrospinal fluid (CSF) of some persons with human immunodeficiency virus (HIV) infection who have undetectable plasma HIV ribonucleic acid (RNA), called CSF viral escape. The CSF HIV Risk Score predicts detection of HIV RNA in the CSF. An elevated risk score suggests who may benefit from CSF HIV RNA monitoring. We examined the association between the CSF HIV Risk Score and CSF viral escape. To improve it's clinical utility, we determined a cut-point that optimized both sensitivity and specificity in predicting CSF HIV viral escape.

**Methods:** Using the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) prospective cohort, a six center, US-based study, we fit generalized estimating equations (GEE) for logistic regression to examine the association between the CSF HIV Risk Score and CSF viral escape among 254 participants at study entry (2004-2007), who were followed through 2009. We determined the cut-point that optimized both sensitivity and specificity, and dichotomized the CSF HIV Risk Score at the selected cut-point (high vs. low). We then fit discrete-time survival models to estimate the incidence and new-onset CSF viral escape over 2,736 person-months.

**Results:** The CSF HIV Risk score at cut-point ≥16 points was associated with a sensitivity of 90.1% (95% Confidence Interval [CI]: 81.8, 96.3) and specificity of 99.1% (95% CI: 97.8, 99.7) for detecting CSF viral escape. The incidence of new-onset CSF viral escape in persons with CSF Risk Scores <16 was 5.1 per 1,000 persons months (95% CI: 2.8, 9.1), compared to 37.6 per 1,000 persons years (95% CI: 24.5, 57.5) when risks scores are high, ≥16, with an adjusted hazard ratio (HR) of
7.97 (95% CI: 3.81, 16.5), $P<0.001$, adjusted for sex, duration of HIV infection, use of protease inhibitor based HIV regimen, substance use disorder and selective serotonin reuptake inhibitor (SSRI) use.

**Conclusion:** The CSF HIV Risk Score may be used as a surrogate to predict CSF viral escape. The utility of the score with suggested thresholds for CSF viral escape will benefit from further research in other populations.
BACKGROUND

Cerebrospinal fluid (CSF) viral escape has been reported in persons with human immunodeficiency infections (HIV) taking combination antiretroviral therapy (cART). CSF viral escape is defined as detectable CSF HIV RNA (>50 copies/mL) in the presence of undetectable plasma HIV RNA (<50 copies/mL) or CSF HIV RNA concentration ≥1 log greater than the plasma HIV RNA concentration (Canestri et al., 2010; Eden et al., 2010; Peluso et al., 2012). The prevalence of CSF viral escape as estimated from a few reports with small sample sizes is about 10%. However the burden of CSF viral escape may be higher than reported.

The 2013 World Health Organization guidelines on HIV treatment emphasizes the use of plasma HIV RNA suppression as the ultimate metric of determining HIV treatment program successes (WHO, 2013). However persistent CNS viral replication occurs in some persons with undetectable plasma HIV RNA. Persistent CNS HIV replication of HIV is associated with neurocognitive impairment, mood disorders and poor HIV prognosis (Garvey, Everitt, Winston, Mackie, & Benzie, 2009; S. L. Letendre, Ellis, Ances, & McCutchan, 2010; Spudich et al., 2011).

In Chapter 3 of this desertion, we developed the CSF HIV Risk Score to predict the probability of identifying detectable CSF HIV RNA in persons on cART. The CSF HIV Risk Score is derived from points assigned to regression units of easily attainable demographic and clinical characteristics retained in a predictive model. Variables included in the CSF HIV Risk Score include plasma HIV RNA, CNS Penetration Effectiveness (CPE) (Letendre et al., 2010), duration of cART, adherence, race and depression status. The CSF HIV Risk Score is capable of
identifying persons with HIV who may benefit from regular and therapeutic CSF testing. The CSF HIV Risk Score would be even more useful if it were able to predict CSF viral escape.

We evaluated the association between the CSF HIV Risk Score and CSF viral escape and determined a cut-point that maximized the sensitivity and specificity of score in predicting CSF HIV viral escape. We also examined the risk of new-onset CSF viral escape associated with CSF HIV Risk Scores above the determined cut-point.

**METHODS**

**Study design and Participants**

CHARTER is a six-center, US-based prospective, observational study initiated in 2004 and designed to comprehensively assess a demographically representative US population who are HIV-seropositive in clinical care (Heaton et al., 2010). The goal of CHARTER is to evaluate the changing presentation of HIV neurological complications in the context of cART. There were no general exclusion criteria in CHARTER except the inability to consent to participation in study assessments. Study sites include Johns Hopkins University, Baltimore, MD; Icahn School of Medicine at Mt. Sinai, New York, NY; University of California, San Diego, CA; University of Texas, Galveston, TX; University of Washington, Seattle, WA; and Washington University, St. Louis, MO. The study was approved by the Institutional Review Board (IRB) or Western IRB for each study site and each participant provided written informed consent.
At study entry, 1561 CHARTER participants, of whom 1,053 were currently on cART, underwent extensive evaluation including HIV and treatment history verified by medical records, physical examination, neuropsychiatric evaluation, neuropsychological testing lumbar puncture, and venipuncture. Thereafter 674 participants who consented to biannual follow-up were selected to undergo follow-up visits every 6 months as part of the longitudinal study component.

For these analyses, we utilized data from the cohort of participants enrolled between 2004 and 2007 and followed through 2009 who completed at least three study visits where lumbar puncture was successfully performed (n=254) (Heaton et al., 2010). Reasons for not completing the lumbar puncture include unsuccessful procedures and participant unwillingness. Because we were interested in determining the incidence of new-onset CSF viral escape, in those analyses, we excluded the 42 participants with CSF viral escape at baseline. There were no differences by socio-demographic or clinical characteristics between participants excluded or retained in these analyses.

**Measures**

The main exposure of interest was the CSF HIV Risk Score. Details of the CSF HIV Risk Score are described in Chapter 3. The CSF Risk Score assigns a probability of detecting CSF HIV RNA in persons with HIV, a higher risk score indicating a higher probability of detecting CSF HIV RNA. The CSF Risk Score was assessed at every study visit and utilized in longitudinal analyses.
The principal outcome variable was CSF viral escape defined as detectable CSF HIV RNA (>50 copies/mL) in the presence of undetectable plasma HIV RNA (<50 copies/mL) or CSF HIV RNA concentration ≥1 log greater than the plasma HIV RNA concentration (Canestri et al., 2010; Eden et al., 2010; Peluso et al., 2012). CSF and plasma HIV RNA concentrations were determined by commercial ultrasensitive reverse transcriptase-polymerase chain reaction (AmpliCor, Roche Diagnostic Systems, Indianapolis, Indiana). CSF viral escape was assessed at each study visit.

Other covariates included in the analyses were major depressive disorder (MDD) by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria assessed using the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) (Kessler & Ustun, 2004). We incorporated both fixed and time-varying covariates in our analysis. The fixed covariates were patient demographic characteristics (age, sex, race, and years of education), self-reported duration of HIV seropositivity, self-reported nadir CD4+ T-cell, lifetime history of DSM-IV MDD, lifetime history of alcohol and substance use disorder assessed by the CIDI, and HCV seropositivity. Time-varying covariates assessed at each study visit included DSM-IV MDD, selective serotonin re-uptake inhibitor (SSRI) use, current CD4+ T-cell count, cognitive impairment assessed by the Global Deficit Score (GDS) (Carey et al., 2004), which summarizes overall functioning across seven constructs from the standardized comprehensive neurocognitive assessment, current cART regimen (protease inhibitor vs. non-nucleoside reverse transcriptase inhibitor based regimen) and duration of cART regimen, CPE score of current cART which is an estimate of the extent to which antiretroviral drugs affect the CNS (Letendre et
al., 2008; Letendre et al., 2010), and medication adherence assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire (Chesney et al., 2000).

**Statistical Analysis**

Population characteristics were examined using summary statistics. We used generalized estimating equations (GEE) for logistic regression with exchangeable correlation structure and robust sandwich-based standard errors to estimate the population-averaged sensitivity and specificity for various cut-points for the association between the CSF HIV Risk score and CSF viral escape (Genders et al., 2012; Zeger, Liang, & Albert, 1988). This approach allows the use of multiple observations per participant over the entire study duration and estimates the marginal effects taking into account the dependence and clustering among repeated measurements for each individual at different occasions (Zeger et al., 1988). We obtained the sensitivity and specificity values by back transforming the natural log of the odds obtained from the various GEE models that were fit. We also fit GEE models to determine the population-averaged odds of CSF viral escape.

We selected a cut-point for the CSF HIV Risk Score by determining which score maximized both sensitivity and specificity in the association with CSF viral escape. The CSF HIV Risk Score was then dichotomized at the selected threshold, high vs. low CSF HIV Risk Score. We fit discrete-time survival models to estimate the incidence rates for the association between the CSF HIV Risk Score (high vs. low category) and new-onset CSF viral escape (Willett & Singer, 1993). Because the exact timing of new-onset CSF viral escape between study visits was not known,
discrete-time survival models treat individuals as being at CSF viral escape for the entire interval between study visits. We fit discrete-time survival models adjusted for sex, duration of HIV infection, use of protease inhibitor based regimen, DSM-IV substance use disorder and selective serotonin reuptake inhibitor (SSRI) use, all of which are not retained component variables of the CSF HIV Risk Score.

We fit our models with the best-fitting functional form of each covariate to ensure robustness. We performed model checking and sensitivity analysis. Statistical analysis was performed by author ERH with *Stata Statistical Software: Release 12.* (College Station, TX: StataCorp LP).

**RESULTS**

Of the 254 persons included in these analyses, the prevalence of CSF viral escape at study entry was 16.5% (n=42). Demographic and clinical characteristics at study entry are presented in *Table 6-1.* Study participants were predominantly male (81.9%), mean age of 44.8 years, and the mean duration of HIV infection mean was 11.5 years with standard deviation (SD) of 5.9 years. At study entry persons with CSF viral escape had higher CSF HIV Risk scores, mean (SD) of 23.0 (8.6) compared to 13.1 (6.1) in persons without CSF viral escape, *P*<0.001 *Table 6-1.*

From GEE models fit at various CSF HIV Risk Score cut-points, a risk score of ≥16 was associated with optimal sensitivity of 90.1% (95% CI: 81.8, 96.3) and specificity of 99.1% (95% CI: 97.8, 99.7) for detecting CSF viral escape *Table 6-2, Figure 6-1.* The likelihood ratio of a positive test at CSF HIV Risk Score cut-point ≥16 is 100.1%. The population averaged odds of CSF viral escape increased by 80% for
each 3-point increase in the CSF HIV Risk Score, Odds ratio (OR)=1.80 (95% CI: 1.65, 1.97); P<0.001 Table6-3, Figure 6-2.

A total of 212 persons without CSF viral escape at study entry, contributing 2,736 persons months, were included in the analyses to estimate the incidence of new-onset CSF viral escape by CSF HIV Risk Score category (high vs. low category), at a cut-point ≥16 Table 6-3. The incidence of new-onset CSF viral escape in persons with CSF Risk Scores <16 was 5.1 per 1,000 persons-months (95% CI: 2.8, 9.1), compared to 37.6 per 1,000 persons years (95% CI: 24.5, 57.5) in persons with risk scores ≥16.

The risk of CSF viral escape was more than 7-fold higher in persons with risk scores ≥16 compared to <16 points, HR=7.97 (95% CI: 3.81, 16.5), P<0.001, adjusted for sex, duration of HIV infection, use of protease inhibitor based HIV regimen, substance use disorder and selective serotonin reuptake inhibitor (SSRI) use Table 6-4. Figure 6-3 shows the cumulative incidence rates for new-onset CSF viral escape over follow-up by risk score category.

**DISCUSSION**

We developed cut-points for the CSF HIV Risk Score that optimize its sensitivity and specificity for detecting CSF viral escape. A cut-point of 16 may be applied to determine which persons would benefit from CSF testing. We determined that CSF HIV Risk Scores ≥16 are associated with more than a 7-fold increase in risk of new-onset CSF viral escape. Because HIV replication in the CSF has been associated with neurocognitive impairment, depression and poor HIV outcomes (Garvey et al., 2009;
Letendre et al., 2010; Spudich et al., 2011), it suggests that monitoring the CSF HIV Risk Score and implementing necessary treatment decisions may provide benefit to reducing the burden of neurocognitive impairment and depression in HIV.

The components of the risk score include plasma HIV RNA, CPE 2.0 of cART, duration of cART, adherence, race and depression status. In line with current treatment guidelines, when increasing trends are observed in CSF HIV Risk Scores, plasma HIV RNA levels need to be checked. Plasma HIV RNA levels >10,000 copies/mL are assigned a risk score of 18 points. In persons on cART who are adhering adequately to treatment, plasma HIV RNA levels >10,000 copies/mL may independently suggest benefits from CSF examination for HIV RNA quantification and genotyping for HIV resistant strains.

In the case of high CSF HIV Risk Score when plasma HIV RNA levels are <10,000 copies/mL (maximum 10 points), other retained variables of the CSF HIV Risk Score contribute sufficiently and independently to the risk of CSF viral escape. It may be of benefit therefore to evaluate, identify and intervene in the modifiable risk factors such as co-morbid depression, adherence and CPE of cART. Because the suggested cut-point of 16 is informed by CSF viral escape, it makes the CSF HIV Risk Score potentially applicable to persons with HIV, whether plasma HIV is detectable or not.

Depression has consistently been associated with HIV (Rabkin, 2008; Sherr, Clucas, Harding, Sibley, & Catalan, 2011; Zanjani, Saboe, & Oslin, 2007). In these analyses (Chapter 5), we determined that the incidence of CSF viral escape in persons with risk score ≥16 was higher than the incidence of CSF viral escape in
persons with depression. Such a finding is expected because CSF HIV Risk Score is a composite of six risk factors including depression.

There are some limitations to consider. The relatively small number of events in the discrete-time survival analysis resulted in wide confidence intervals. However incidence rates for high vs. low CSF HIV Risk Score category were significantly different. Because the predictive value of a test is related to disease prevalence (Vecchio, 1966), consideration must be given to the various target populations in which the proposed cut-point is used. However by maximizing specificity at a cut-point of 16 (99.1%), we minimize the false-positive rate.

The strengths of these analyses include the use of the GEE approach to estimate the sensitivity and specificity as a weighted average across the study population. The weighted population averaged estimate helps to account for transient increases in CSF HIV RNA levels over time. The GEE approach enables us to use multiple observations per participant and accounts for correlated data with each participant. Because assessment of CSF viral escape is clustered within a patient, by accounting for this correlation, we avoid misleading small standard errors and 95% CIs. We were also able to show in these analyses, for the first time, that a surrogate of detectable CSF HIV RNA (the CSF HIV Risk Score) is associated with CSF viral escape. The use of this score and clinical applicability of the suggested threshold of 16 points may benefit from external validation in subsequent trials or in existing databases.

In conclusion, the CSF HIV Risk Score may be used as a surrogate to predict CSF viral escape. The utility of the score with suggested thresholds for CSF viral
escape needs to be extended to other populations. We speculate that the CSF HIV
Risk Score may help to reduce the burden of neuropsychiatric complications of HIV
and may be a resource saving measure by helping to determine which persons
would benefit most from CSF testing.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N=254)</th>
<th>CSF Viral Escape</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes n= (42)</td>
<td>n= (212)</td>
<td></td>
</tr>
<tr>
<td>CSF HIV Risk Score, mean (SD)</td>
<td>14.8 (7.7)</td>
<td>23 (8.6)</td>
<td>13.1 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, mean (SD) yrs</td>
<td>44.8 (7.6)</td>
<td>42.6 (9.6)</td>
<td>45.3 (7.0)</td>
<td>0.034</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>208 (81.9)</td>
<td>37 (88.1)</td>
<td>171 (80.7)</td>
<td>0.253</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>109 (42.9)</td>
<td>12 (28.6)</td>
<td>97 (45.8)</td>
<td>0.095</td>
</tr>
<tr>
<td>Black</td>
<td>108 (42.5)</td>
<td>21 (50.0)</td>
<td>87 (41.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic and Other</td>
<td>37 (14.6)</td>
<td>9 (21.4)</td>
<td>28 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD) yrs</td>
<td>12.8 (2.3)</td>
<td>12.6 (1.9)</td>
<td>12.9 (2.4)</td>
<td>0.440</td>
</tr>
<tr>
<td>Log plasma RNA, mean (SD)</td>
<td>1.54 (1.65)</td>
<td>3.26 (1.79)</td>
<td>1.20 (1.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log CSF HIV RNA, mean (SD)</td>
<td>0.55 (1.01)</td>
<td>2.45 (0.92)</td>
<td>0.17 (0.44)</td>
<td></td>
</tr>
<tr>
<td>Current CD4, mean (SD)</td>
<td>476.7 (281.5)</td>
<td>399.4 (263.1)</td>
<td>492.0 (283.1)</td>
<td>0.051</td>
</tr>
<tr>
<td>CD4 nadir, mean (SD)</td>
<td>145.5 (133.4)</td>
<td>165.6 (156.0)</td>
<td>141.4 (128.5)</td>
<td>0.287</td>
</tr>
<tr>
<td>cART Regimen, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI-based regimen</td>
<td>155 (61.0)</td>
<td>34 (81.0)</td>
<td>121 (57.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-PI based regimen</td>
<td>99 (39.0)</td>
<td>8 (19.1)</td>
<td>91 (42.9)</td>
<td></td>
</tr>
<tr>
<td>cART Regimen, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>141 (55.5)</td>
<td>32 (76.2)</td>
<td>109 (51.4)</td>
<td>0.019</td>
</tr>
<tr>
<td>NNRTI</td>
<td>88 (34.7)</td>
<td>6 (14.3)</td>
<td>82 (38.7)</td>
<td></td>
</tr>
<tr>
<td>PI-NNRTI</td>
<td>14 (5.5)</td>
<td>2 (4.8)</td>
<td>12 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (4.3)</td>
<td>2 (4.8)</td>
<td>9 (4.3)</td>
<td></td>
</tr>
<tr>
<td>CPE 2.0, median (range)</td>
<td>7.8 (2.0)</td>
<td>7.2 (2.0)</td>
<td>7.9 (1.8)</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>≥95%</td>
<td>221</td>
<td>(87.0)</td>
<td>31</td>
<td>(76.2)</td>
</tr>
<tr>
<td>85-94%</td>
<td>18</td>
<td>(7.1)</td>
<td>2</td>
<td>(4.8)</td>
</tr>
<tr>
<td>&lt;85%</td>
<td>15</td>
<td>(5.9)</td>
<td>8</td>
<td>(19.1)</td>
</tr>
<tr>
<td>HIV Duration, mean (SD), yrs.</td>
<td>11.5</td>
<td>(5.9)</td>
<td>9.6</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Current DSM-IV MDD, n (%)</td>
<td>31</td>
<td>(12.2)</td>
<td>8</td>
<td>(19.1)</td>
</tr>
<tr>
<td>Lifetime DSM-IV MDD, n (%)</td>
<td>134</td>
<td>(52.8)</td>
<td>28</td>
<td>(66.7)</td>
</tr>
<tr>
<td>Lifetime alcohol abuse, n (%)</td>
<td>71</td>
<td>(28.0)</td>
<td>11</td>
<td>(26.2)</td>
</tr>
<tr>
<td>Lifetime substance abuse, n (%)</td>
<td>85</td>
<td>(33.5)</td>
<td>9</td>
<td>(21.4)</td>
</tr>
<tr>
<td>Cognition, GDS, median (IQR)</td>
<td>0.48</td>
<td>(0.48)</td>
<td>0.31</td>
<td>(0.37)</td>
</tr>
<tr>
<td>Prior HCV infection, n (%)</td>
<td>71</td>
<td>(28.4)</td>
<td>9</td>
<td>(22.5)</td>
</tr>
<tr>
<td>Prior Opportunistic infection, n (%)</td>
<td>41</td>
<td>(14.1)</td>
<td>6</td>
<td>(42.9)</td>
</tr>
</tbody>
</table>

cART: Combination antiretroviral therapy; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; CPE 2.0: CNS penetration effectiveness score 2.0; Adherence assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire; Lifetime depression assessed by DSM-IV using the Composite International Diagnostic Interview (CIDI); Lifetime alcohol and substance use disorder assessed by DSM-IV CIDI; GDS: Global Deficit Score; MDD: Major depressive disorder; SD: standard deviation; IQR: inter-quartile range; P-value assessed by chi-square for categorical variables and t-test for continuous variables; *p<0.05
Table 6-2. Diagnostic Properties of the CSF HIV Risk Score at Various Cut-Points of the CSF HIV Risk Score

<table>
<thead>
<tr>
<th>CSF HIV Risk Score Cut-Point</th>
<th>Sensitivity (95% CI)%</th>
<th>Specificity (95% CI)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>99.9 (98.4, 100.0)</td>
<td>65.3 (62.7, 68.3)</td>
</tr>
<tr>
<td>11</td>
<td>99.8 (97.8, 100.0)</td>
<td>70.7 (67.5, 74.3)</td>
</tr>
<tr>
<td>12</td>
<td>99.9 (94.4, 99.9)</td>
<td>81.2 (77.3, 85.1)</td>
</tr>
<tr>
<td>13</td>
<td>97.2 (91.2, 99.5)</td>
<td>90.8 (87.2, 93.8)</td>
</tr>
<tr>
<td>14</td>
<td>94.3 (86.9, 98.5)</td>
<td>95.9 (93.2, 97.8)</td>
</tr>
<tr>
<td>15</td>
<td>91.3 (83.0, 97.0)</td>
<td>98.2 (96.5, 99.3)</td>
</tr>
<tr>
<td>16</td>
<td><strong>90.1 (81.8, 96.3)</strong></td>
<td><strong>99.1 (97.8, 99.7)</strong></td>
</tr>
<tr>
<td>17</td>
<td>88.4 (79.8, 95.2)</td>
<td>99.4 (98.4, 99.8)</td>
</tr>
<tr>
<td>18</td>
<td>88.4 (79.8, 95.2)</td>
<td>99.7 (98.9, 99.9)</td>
</tr>
<tr>
<td>19</td>
<td>86.4 (78.1, 93.7)</td>
<td>99.9 (99.7, 100.0)</td>
</tr>
<tr>
<td>20</td>
<td>83.5 (75.6, 91.1)</td>
<td>100.0 (99.9, 100.0)</td>
</tr>
</tbody>
</table>

Likelihood ratio of a positive test at CSF HIV Risk Score cut-point of 16 is 100.1%; Likelihood ratio of a negative test at CSF HIV Risk Score cut-point of 16 is 0.1%
Table 6-3. Population Averaged Odds Ratios for the Association Between the CSF HIV Risk Score and CSF Virologic Failure by Generalized Estimating Equations, N=254

<table>
<thead>
<tr>
<th>CSF HIV Risk Score, per point increase</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (continuous)</td>
<td>1.22</td>
<td>1.18, 1.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>1.80</td>
<td>1.65, 1.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>2.67</td>
<td>2.31, 3.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7</td>
<td>3.95</td>
<td>3.21, 4.87</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CSF: Cerebrospinal fluid; HIV: Human Immunodeficiency Virus
Table 6-3. Incidence Rates for New-Onset Cerebrospinal Fluid Viral Escape Based on the Cerebrospinal Fluid Risk Score Cut-points by Discrete-time Survival Models, N=212

<table>
<thead>
<tr>
<th>New-Onset CSF Viral Escape</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Time at Risk (Person-months)</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Entire study cohort</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CSF HIV Risk Score</td>
</tr>
<tr>
<td>&lt;16 points</td>
</tr>
<tr>
<td>&gt;=16 points</td>
</tr>
</tbody>
</table>

CSF: Cerebrospinal Fluid Risk; CSF HIV Risk Score suggested cut-point of 16 points for optimum test properties.
**Table 6-4.** Hazards Ratios for the Association Between the CSF HIV Risk Score (cut-point 16) and CSF Viral Escape by Discrete Time Survival Models, N=212

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>(95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>7.63</td>
<td>(3.76, 15.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>7.97</td>
<td>(3.81, 16.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CSF: Cerebrospinal Fluid; *Hazard ratios adjusted for sex, duration of HIV infection, use of protease inhibitor based HIV treatment, Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) substance use disorder and selective serotonin reuptake inhibitor (SSRI) use.
Figure 6-1. Sensitivity and Specificity Plots for CSF Viral Escape at Various Cut-points of the CSF HIV Risk Score

![Graph showing sensitivity and specificity plots for CSF HIV risk score cut-points (Sens = 90.1%, Spec = 99.1%, PPV = 95.6%, LR+ = 100%)](image)

CS: Cerebrospinal fluid; HIV: Human Immunodeficiency Virus
Diagnostic performance of proposed cut-point of 16 displayed as insert.
Figure 6-2. Odds Ratios for the Association Between Various Increases in CSF Risk Score and CSF Viral Escape

CSF: Cerebrospinal fluid; HIV: Human Immunodeficiency Virus
Figure 6-3. Cumulative Incidence Rates for New-Onset CSF Viral Escape by CSF HIV Risk Score Category (<16 vs. >=16 points), N=212

CSF: Cerebrospinal Fluid
References


for quantifying antiretroviral penetration into the central nervous system.

*Archives of Neurology, 65*(1), 65-70. doi:10.1001/archneurol.2007.31


CHAPTER 7

SUMMARY AND PUBLIC HEALTH SIGNIFICANCE
SUMMARY

This dissertation sought to investigate if better CNS penetration of antiretroviral therapy is associated with lower rates of depression independently of cognitive impairment. We hypothesized that better CNS penetration assessed by the CNS penetration effectiveness (CPE) score, is associated with lower levels of depression. The auxiliary hypothesis was that better penetration of cART is associated with higher therapeutic drug levels in the CNS and results in lower levels or undetectable HIV RNA in the CSF (Cusini et al., 2013). This dissertation utilized data from the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) prospective cohort study, which is uniquely enriched by the bi-annual CSF exams that study participants undergo (Heaton et al., 2010).

In Chapter 3 we first determined if the CPE score (Letendre, Ellis, Ances, & McCutchan, 2010), an estimate of the CNS penetration of antiretroviral therapy was able to predict persons who would have detectable HIV RNA in the CSF. The CPE was limited in discriminating ability of persons with detectable CSF HIV RNA at a threshold of >50 copies/mL. We therefore developed a new risk score to predict the probability of identifying detectable CSF HIV RNA in persons on cART utilizing readily available clinical and demographic characteristics. The CSF HIV Risk Score ranges from 0 to 42, a higher score suggesting increased probability of detectable CSF HIV RNA. The CSF HIV Risk Score has good calibration and discrimination, and may provide a meaningful tool to discuss the utility of performing a lumbar puncture.
In Chapter 4 we determined that detectable CSF HIV RNA was not only associated with a higher prevalence of depression, but also associated with a 4-fold increased risk of new-onset moderate-to-severe depressive symptoms. This finding helps to bring the scientific community a step closer to understanding the pathophysiological changes that underlie depression in persons with HIV.

An equally interesting finding in Chapter 5 was that depression in persons with HIV is associated with higher incidence of new-onset detectable CSF HIV RNA when plasma HIV RNA is undetectable, known as CSF viral escape (Canestri et al., 2010; Eden et al., 2010). Our findings provide further evidence that aside from the increased risk behavior and lower treatment adherence in persons who are depressed, depression may alter the immune mechanisms through various processes in favor of increased CNS HIV replication. In this chapter we also provide the first representative burden of CSF viral escape: prevalence of 17.6% and incidence of 11.7 per 1,000 person-months.

The CSF Risk Score at a threshold of ≥16 points may be employed in clinical practice as a cut-point to inform decisions about performing a lumber puncture to examine CSF in persons with HIV. We evaluated and suggest the use of a cut-point of ≥16 on the CSF HIV Risk Score in Chapter 6, where we examined the association between the CSF HIV Risk Score and CSF viral escape. At a cut-point ≥16, the CSF HIV Risk Score displayed sensitivity of 90.1% and specificity of 99.1%. Persons with risk scores ≥16 have over 7-fold increase in risk of new-onset CSF viral escape compared to person with risk scores <16.
PUBLIC HEALTH SIGNIFICANCE AND FUTURE DIRECTIONS

This dissertation contributes to scientific knowledge by providing estimates of the burden of CSF viral escape, and evidence of increased risk of depression in persons with detectable CSF HIV RNA. This works lays down the framework for potential advances in investigating the bidirectional relationship between depression and HIV. It also provides a clinical tool, the CSF HIV Risk Score, which may have a positive impact on HIV care worldwide.

Immune Mediators of Depression in HIV

We have showed in this dissertation that detectable CSF HIV RNA is associated with increased risk of depression. One mechanism by which HIV may result in increased risk of depression is through alteration of the immune system (Raison et al., 2009; Raison et al., 2010). A logical next step would be to evaluate changes in the inflammatory and trophic environment of the CNS and peripheral blood as pertains to the extent of penetration of cART. Such evaluation would illuminate potential neuroinflammatory mediators of depression and improve our understanding of the neurobehavioral effects of cART with respect to their extent of CNS penetration. We hypothesize that detectable CSF HIV RNA as well as lower CNS penetration of cART would be associated with increased CSF and blood cytokines such as tumor necrosis factor-alpha, Interleukin-1, -6, -12 and monocyte chemo attractant protein-1, and which would be associated with depression and neurocognitive impairment in HIV. This undertaking will improve our understanding of the neuropathogenesis of HIV and the neurobehavioral effects of cART. The potential benefits of such future
research include improvement in therapeutic choices for patients with HIV/AIDS, provide insight into drug development, and thereby improve clinical outcomes.

**Guidelines for Testing Cerebrospinal Fluid in Managing HIV**

In this dissertation we provide the first representative estimates of the burden of CSF viral escape. Our findings suggest the persistent CSF viral replication occurs in more persons than previously estimated. CSF viral escape is associated with depression and neurocognitive impairment which if not adequately addressed, may fuel an epidemic of neurocognitively impaired and depressed persons with HIV.

Because over 33 million persons with HIV (UNAIDS, 2010), and persons with HIV are living longer, the population attributable risk of the consequences of CSF viral escape cannot be ignored. However there are currently no guidelines for testing CSF in managing HIV–associated neurocognitive disorders in the United States as there are in Europe (European AIDS Clinical Society, 2012). Recently sixty-six experts from 30 countries, The Mind Exchange Program, recommended CSF testing for HIV RNA in persons with suspected or demonstrated neurocognitive symptoms (Mind Exchange Working Group, 2013). Such guidelines are long overdue and future endeavors need to focus on developing compelling data and scientific arguments to advocate for CSF testing guideline for managing HIV.

As part of this endeavor, efforts aimed at monitoring outcomes such as mood, cognition and inflammatory markers as part of clinical trials that incorporate CSF testing may be useful. We hypothesize that routine testing of CSF for HIV RNA quantities and genotyping for resistant HIV strains in persons for whom it is
warranted will improve HIV outcomes. Such measures may eventually lead to a decrease in health care cost as persons with HIV continue to live longer because of improved care.

**Treating Depression in HIV Effectively**

Our findings add to the consistent evidence that depression is associated with poor HIV control and outcomes (Cook et al., 2004; Ickovics et al., 2001; Whetten et al., 2006). This dissertation is however the first report on the association between depression and increased risk of CSF viral escape. Depression in HIV is a modifiable risk factor for poor HIV outcomes and can be effectively treated with psychotropic medications, psychological interventions and by cognitive-behavioral therapy (Sherr, Clucas, Harding, Sibley, & Catalan, 2011; Treisman & Angelino, 2004). Every effort must therefore be made to identify and treat depression in persons who are at highest risk. There remains a synergetic relationship between HIV/AIDS and depression. Depression increases the risk of acquisition and transmission of HIV and is associated with poor HIV control including CSF viral escape. HIV/AIDS on the other hand, increases the risk of depression, a finding further corroborated by this dissertation, which to our knowledge is the first report of the association between detectable CSF HIV RNA and increased depression.

We propose a bidirectional relationship between depression and HIV **Figure 7-1**. The depression → HIV/AIDS association may be related to factors such as increased sexual risk behavior and substance use disorders. Factors that may drive the HIV/AIDS → depression association include CNS penetration, CNS viral
replication, stigma, genetic contributions and family history (Alvy et al., 2011; Chander, Himelhoch, & Moore, 2006; DiMatteo, Lepper, & Croghan, 2000; Hutton, Lyketsos, Zenilman, Thompson, & Erbelding, 2004; Simbayi et al., 2007). Access to care and adherence may affect the depression-HIV/AIDS association in either direction.

An extension of our findings would be to demonstrate efficacy in clinical trials, that treating depression will reduce transmission and acquisition of HIV, and improve HIV control. We hypothesize that the use of depression screening tools and checklists in management of HIV will identify persons at risk for depression, and that adequate treatment will improve HIV outcomes. Observational studies may also be useful in assessing the effectiveness of treating depression as a strategy for better HIV management.

**Utility of the Cerebrospinal Fluid Risk Score**

In this dissertation, we developed the first risk score to predict detectable CSF HIV RNA at a threshold of 50 copies/mL. The CSF HIV Risk Score displayed good discrimination and calibration. We suggest a threshold of 16 points to guide decisions for a lumbar puncture to test CSF. Because this threshold is informed by CSF viral escape, it makes the CSF HIV Risk Score also potentially applicable to persons with undetectable plasma HIV RNA. Although we validated the development of the CSF HIV Risk Score using two robust internal validation techniques, external validation of the score is helpful to determine whether recalibration of the score is necessitated for use in other populations.
We describe a robust relationship between higher CSF HIV Risk Scores and increased CSF viral escape. Future research efforts should be directed to evaluate if a baseline assessment of the CSF HIV Risk Score is associated with developing cognitive impairment or depression in the future. Such findings will provide further evidence for regular monitoring of CSF HIV Risk Scores in persons with HIV. We hypothesize that regular monitoring of the CSF HIV Risk Score to help prompt the needed medical intervention will improve management of HIV. In resource limited locations throughout the world, the use of the CSF HIV Risk Score to guide treatment may be a useful surrogate that could prevent several HIV CNS complications.

Clinical trials may help to demonstrate the utility and applicability of the CSF HIV Risk Score. Cost savings and resource saving benefits from the use of the CSF HIV Risk Score can be determined from both observational and clinical trials. The CSF HIV Risk Score is a surrogate of CNS activity and its use may help to improve HIV management and reduce CNS complications.
Figure 7-1. Conceptual Framework of the Bi-directional Association Between Major Depressive Disorder and HIV/AIDS

IDO: Indoleamine 2,3-dioxygenase; CNS: Central Nervous System; HIV: Human Immunodeficiency Virus; RNA: Ribonucleic acid
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UNAIDS.UNAIDS report on the global AIDS epidemic.

CURRICULUM VITAE
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EDUCATION AND TRAINING
Undergraduate: Bachelor of Medicine and Surgery (MBChB) March 2000
University of Ghana Medical School, Accra

Graduate: Master of Public Health (MPH) May 2004, Epidemiology and Biostatistics
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Doctor of Philosophy (PhD), Epidemiology, (Expected 2013)
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

PROFESSIONAL EXPERIENCE
2013– Research Analyst, Department of Psychiatry, Johns Hopkins School of Medicine

Institute, Baltimore, MD

2010-2012 Systematic Reviewer/Epidemiologist, SAIC (for National Heart, Lung and Blood
Institute, NHLBI), Rockville, MD

2006–2010 Senior Coordinator of Clinical Research, Departments of Neurology and
Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD

2004-2005 Research Assistant, Department of Epidemiology, Johns Hopkins Bloomberg
School of Public Health, Baltimore, MD

2001-2003 Medical Officer, Departments of Hematology and Oncology, University of Ghana
Medical School, Korle Bu Teaching Hospital, Accra

2000-2001 House Officer, Departments of Medicine and Surgery, University of Ghana Medical
School, Korle Bu Teaching Hospital, Accra, Ghana

CONSULTING
2012 Biogen Idec, Cambridge, MA
Evaluate and Develop Staging System for a Neurologic Disease

2007-2008 Accentia Biopharmaceuticals, Tampa, FL
Phase III Clinical trial design for Commercial Development of Therapeutic Agent as
approved FDA products
2005-2006  HCD International Lanham, MD  
_Developed Health Journalism Training Modules for Journalists in Africa, Voice of America Funded Project_

PROFESSIONAL AFFILIATIONS

American Public Health Association, Member  
American Association for the Advancement of Science, Member  
Transverse Myelitis Association, Member  
African Public Health Network, Johns Hopkins School of Public Health; Past President

EDITORIAL ACTIVITIES

Peer reviewer- JAMA Neurology

TEACHING/EDUCATION

2011-2013  Lead Teaching Assistant, Principles of Epidemiology  
Johns Hopkins Bloomberg School of Public Health

2011-2012  Teaching Assistant, Epidemiologic Methods 2, Epidemiologic Methods 3  
Johns Hopkins Bloomberg School of Public Health

2004-2005  Lead Teaching Assistant, Current Issues in Public Health  
Johns Hopkins Bloomberg School of Public Health

_Lectures_

Review Lecture, _Principles of Epidemiology_, Johns Hopkins Bloomberg School of Public Health, August 2013

Review Lecture, _Principles of Epidemiology_, Johns Hopkins Bloomberg School of Public Health, August 2012

AWARDS

Meritorious Service Award for Dedicated and Outstanding Service towards Excellence in Medical Practice, University of Ghana Medical School, Korle Bu Teaching Hospital, 2002

Teaching Assistant Recognition Award for Outstanding Service, Johns Hopkins Bloomberg School of Public Health, 2012

PUBLICATIONS


The Cerebrospinal Fluid Risk Score for Assessing Central Nervous System HIV Activity. *(Under review)*


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