DEPRESSION AND HIV INFECTION:

RISK FACTORS FOR CARDIOVASCULAR DISEASE

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ABSTRACT

Depression, a common mental health disorder, is associated with higher risk of cardiovascular disease (CVD). Adults with HIV infection are often burdened with depression. Although both depression and HIV infection are risk factors for CVD, previous studies have not explored how co-occurring depression and HIV are associated with CVD outcomes or underlying physiology. The aim of this dissertation was to (i) measure the risk of incident heart failure (HF) with co-occurring major depressive disorder (MDD) and HIV infection; (ii) measure biomarkers of inflammation, coagulation, monocyte activation, and metabolism with depression and HIV infection; and (iii) provide a comprehensive biomarker profile associated with symptoms of major depression in HIV+ and HIV- participants. We analyzed data from the Veterans Aging Cohort Study (VACS), a prospective study of HIV+ and HIV- veterans matched on age, sex, race/ethnicity, and geographical region. In a sample of 81,427 participants, we found that those with co-occurring HIV infection and MDD had significantly higher risk of incident HF compared to HIV- participants without MDD, after adjusting for covariates. In a subset of 2,099 participants, we determined that depression was associated with higher concentrations of interleukin-6 and soluble CD14 (biomarkers for inflammation and monocyte activation) in HIV- participants but not HIV+ participants. HIV+ participants had higher concentrations of glucose and triglycerides and lower concentrations of high-density lipoprotein cholesterol with depression. In a smaller sample with more extensive biomarker data, we found a significant

association between depression and lower concentrations of vascular endothelial growth factor in HIV+ participants. Neither biomarker study supported the hypothesis that co-occurring depressive symptoms and HIV infection would interact and produce excessively high concentrations of these biomarkers. The findings from this dissertation are significant for public health research and practice. Depression is extremely common and is a risk factor for CVD. In the future, investigators must elucidate specific mechanisms driving CVD risk with depression and identify effective therapies for preventing depression-related CVD morbidity and mortality in both HIV- and HIV+ adults. Meanwhile, clinicians must remain vigilant in identifying and managing depressive symptoms, especially among those who are at heightened risk for CVD due to HIV infection.

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1.0 INTRODUCTION

The idea for this dissertation stemmed from three inter-related observations in the literature. First, depression is associated with cardiovascular disease (CVD). Second, HIV infection is also associated with CVD. Third, depression is common among those with HIV infection. Individuals with depression and individuals with HIV infection may share unhealthy behaviors that put them at higher risk for CVD. Alternatively, depression and HIV infection may cause subclinical changes, such as changes in biomarker concentrations, which could put them at higher risk for CVD. The following sections describe key papers in three areas: (1.1) depression and cardiovascular disease; (1.2) HIV infection and cardiovascular disease; and (1.3) depression and HIV infection. These studies are summarized in tables found in Appendix A.

1.1 DEPRESSION

Depression is highly prevalent in the United States (4.4 to 20% of the general population) and is responsible for a great deal of disability worldwide.[1] Symptoms of this disorder include absence of pleasure, motivation, or interest in daily life, feelings of guilt, lack of concentration, poor self-esteem, sleep disturbances, and altered appetite.[2] Depressive symptoms range from mild to severe and can be transient or chronic. Clinical depression, which includes major depressive disorder (MDD) and dysthymic disorder, is diagnoses by clinicians who conduct formal in-

person interviews. Treatment for depression may include pharmacological or behavioral therapy.

Depression is associated with cardiovascular disease events, including acute myocardial infarction, heart failure, and stroke.[3] Many systemic changes occur in response to chronic stress and depression. Biomarkers used to measure growth factor, inflammation, immune activation, endocrine function, and metabolism are altered with depression and thought to be potential mediators of its association with CVD.[4] In addition to physiological changes, depression enhances maladaptive behavioral changes, such as decreased treatment adherence, decreased physical activity, and poor dietary habits, which are also risk factors for cardiovascular disease.[3]

1.1.1 Pathophysiological mechanisms

Depression is associated with systemic damage to multiple organ systems.[2] Many previous investigators have identified depression as a risk factor for cardiovascular disease, metabolic disorder, blood coagulation, overactive stress and endocrine response, inflammation, neurogenerative changes, and unhealthy behaviors. Due to the significant impact of depression on human life, the World Health Organization declared depression as the leading cause of disability.[2] The following paragraphs describe common changes seen in a depressed state.

Cardiovascular disease The physiological associations between depression and cardiovascular disease are multifactorial. After a series of upstream changes that occur outside the cardiovascular system (described in the following paragraphs), the blood vessels may experience increased sympathetic tone, increased vascular resistance, increased blood viscosity, increased intima-media thickness, and atherosclerosis, which each contribute to increased blood pressure.[2] These changes are well-known risk factors for coronary artery disease, myocardial infarction,

stroke, and heart failure. With depression, the heart also experiences increased heart rate and decreased heart rate variability, which are both associated with left ventricle dysfunction and heart failure.[2, 5] [Note: The review article by Nemeroff & Goldschmidt-Clermont (2012) provides a helpful figure that illustrates the mechanisms associated with depression and CVD[5]] The following paragraphs describe upstream mechanisms that lead to changes in the cardiovascular system.

Metabolic disorder Biochemical mechanisms exist to manage glucose and lipid levels within the blood stream. When glucose and lipids are poorly controlled, these metabolites accumulate and increase the risk for plaque development, obesity, insulin resistance, and diabetes.[6] These conditions, which tend to cluster together and are referred to as metabolic syndrome, increase risk for hypertension, coronary heart disease, heart attack, and death. Depression is associated with obesity, insulin resistance, poor glucose regulation, and diabetes.[2] The association between depression and obesity or diabetes may be bidirectional.

Blood coagulation Platelets, which play an essential role in coagulation, are thought to be involved in the association between depression and ischemic heart disease due to increased platelet activation during a stress response.[7] Elevated cortisol levels increase the rate in which platelet surfaces adhere to collagen within the endothelial lining of the vascular wall. This process activates the platelet and causes receptors to bind with fibrinogen. The activated platelet secretes the contents of its intracellular granules, which enhances aggregation with additional platelets. Clotting increases risk for ischemic events.

Observational and randomized clinical trials suggest that selective serotonin reuptake inhibitors (SSRIs; an antidepressant) reduce platelet activation.[7] Platelet activation can be quantified by measuring the concentration of two components of platelet granules, beta-

thromboglobulin and platelet factor 4, which are released into the plasma during platelet activation. In a randomized clinical trial, six weeks of therapy using the SSRI parosetine was associated with decreased beta-thromboglobulin and platelet factor 4 levels among depressed ischemic heart disease patients compared to comparators who used nortriptyline, which is in the antidepressant class of drugs call non-selective tricyclic antidepresseants (TCAs).[8] The SADHART study looked at another SSRI, sertraline, and found significantly lower levels of beta-thromboglobulin in the treatment group compared to the group that received a placebo.[9] As with any anticoagulant, SSRI use is associated with a risk for excess bleeding.[7] Overall risk of morbidity or mortality from bleeding should be considered when evaluating the true benefits of SSRI for CVD health.

Overactive endocrinological / stress response External stress is responsible for stimulating the hypothalamus-pituitary-adrenal gland (HPA) axis.[2] Specifically, both corticotrophin-releasing hormone (CRH) and arginine vasopressin are released in response to stress, which release corticotrophin into the peripheral circulatory system and stimulate the release of corticosteroid from the adrenal cortex. Chronic activation of the HPA axis can lead to downstream complications such as elevated blood pressure, elevated heart rate, decreased heart rate variability, and platelet activation.

Inflammation Investigators have observed an association between depression and activation of the immune system and documented elevated levels of pro-inflammatory cytokines among individuals with depression.[2] A 2010 meta-analysis summarized twenty-four studies that compared cytokine concentrations between individuals with major depressive disorder and controls.[1] The two inflammatory cytokines that were significant in the weighted meta-analysis were interleukin-6 and TNF-alpha.

Unhealthy behaviors Depression is often associated with unhealthy behaviors including poor diet, smoking, and inactivity, which are each associated with metabolic syndrome, CVD, and death.[6]

1.1.2 Depression and heart failure

Compared to the literature describing the association between depression and ischemic CVD events, few studies describe the association between depression and heart failure (HF) and no meta-analyses exist. This section summarizes nine studies that describe the association between depression and heart failure (Table 6-1). Eight of the nine studies assessed over 500 participants. Overall, majority of the participants were elderly and female. Eight of the nine studies included participants with a mean age over 57 years, while five of the studies had a mean age over 70 years. The one study that made a comparison of depression in a younger group of participants (mean age = 38 years) investigated a subclinical measure of heart failure.[10] Three of the studies included only women, while five of the six remaining studies included slightly more women than men.

The methods for defining depression were variable. In fact, eight unique definitions were used in the nine studies. All nine studies used self-assessment scales to assess severity of depressive symptoms as part of their definition. "Depression" was defined with four different scales and seven different cut-off criteria. Additionally, two studies included a formal diagnosis of clinical depression based on a formal interview of the study participant by a trained healthcare professional. The measures for identifying HF also ranged in methodology. Methods for assessing HF status ranged from adjudicated hospital records by a team of health care professionals to self-reported history of HF-related symptoms by participants.

The original paper to consider the association between depression and HF was by Whooley *et al*. in 1998.[11] The outcome of this study was mortality due to congestive HF based on hospital records and death certificates. The risk for HF mortality was more than three-times higher in those who scored high on the Geriatric Depression Scale compared to those who had lower scores. A limitation to this study was that it did not have data regarding CV events over the lifecourse. Therefore, it is not clear whether these HF deaths were preceded by ischemic CVD events. Nonetheless, the findings of this paper sparked the interest of several investigators to assess the significance of incident HF with depression.

In 2001, Abramson *et al*. published findings from the first large scale study to specifically understand the association between depression and incident HF.[11] Their study investigated incident HF over a mean of 4.5 years in 4,538 older adults with isolated systolic hypertension and reported 2.59 times greater risk in individuals with a baseline Center for Epidemiologic Study Depression Scale (CES-D) score $\geq$ 16 compared to those with a score below 16, after adjusting for MI. The findings emphasized that individuals are at risk for HF independently from ischemic CVD events. A subsequent study of elderly individuals found gender differences in the association between depression and HF.[12] Williams *et al*. used a cut-point of 21 on the CES-D scale and reported that incident HF was significantly higher in women with depression compared to non-depressed women (HR = 1.96; 95% CI, 1.11 – 3.26). The association was not significant in men (HR = 0.62; 95% CI, 0.23 – 1.71). A third study reported a significantly higher risk of HF with depression defined using cut-off points using the BDI scale, but the analysis was considered exploratory due to too few events.[13]

Two studies did not find a significant risk of HF with depression.[14, 15] One of these studies was conducted in 1,749 participants.[14] Individuals with a baseline CES-D score $\geq$ 16

were not at higher risk of HF (p = 0.65). The second study was conducted in the Netherlands and used both the DSM-III Criteria for major depressive disorder (MDD) and the CES-D score to identify depression.[15] Incident HF was based on self-reported symptoms, medications, or a previous diagnosis. To obtain adequate power, the HF outcome was lumped with arrhythmia, which created a "non-ischemic CVD" group. The association between MDD and non-ischemic CVD was not significant in this cohort (RR = 0.96; 95% CI 0.24 – 3.89).

Two of the studies provided subclinical measures of HF (respiratory gas exchange endpoints and left ventricular changes).[10, 16] Depression was associated with decreased ventilatory efficiency (p = 0.0012), increased left ventricle mass (p = 0.019), and decreased early diastolic velocity (p = 0.006). Ventilatory inefficiency is a sign that the heart is beginning to fail at effectively pumping oxygenated blood through the circulation. Larger left ventricle (LV) mass is related to narrowing of the LV chamber, which could precede diastolic HF.

The final two studies reported associations between depression and biomarkers.[13, 17] Vaccarino *et al*. assessed the C-reactive protein (CRP) and interleukin-6 (IL-6) concentrations of participants categorized into three levels of depression.[13] The trend across levels revealed a significant increase in CRP and IL-6 with more severe depression ($p < 0.0001$ and p = 0.0008, respectively). Although significant, these inflammatory biomarkers explained only a small proportion of the association between depression and CVD, which indicates the underlying mechanism likely involves pathways other than inflammation. In HF, collagen is deposited in the myocardium and fibrosis occurs.[16] Kim *et al*. reported that depression was associated with increased procollagen type I (OR = 1.43; 95% CI 1.00 – 2.03), again suggesting that HF may advance with depressive symptoms.

Since these studies sampled older adults, the findings are not generalizable to a younger population. However, HF tends to develops with age, and majority of HF patients are over 65 years.[18] Thus, it was justifiable for these studies to be directed at older individuals, and the findings remain meaningful in that population. In three of the four studies reporting subclinical markers of HF, the mean age of participants was less than 60 years. Considering subclinical disease precedes clinical manifestations, it makes sense for these studies to sample younger populations.

With the large number of elderly participants included in these studies, survivor bias may have influenced some of these findings. Women have a longer life expectancy compared to men. Therefore, the study that found significant risk of HF in women but not men may be due to artifact from survivor bias.[12] In other words, the men with HF may have died before enrolling in the study, potentially biasing the findings towards the null.

Across these studies, methods for measuring exposure and outcome variables were not standardized. The CES-D is feasible to administer in a large cohort and provides information about the presence of depressive symptoms, but the findings are not equivalent to a diagnosis of clinical depression.[11, 12] The outcome definitions for HF diagnosis also ranged in sensitivity and specificity, which may have resulted in misclassification. Despite differences in measurement, however, the trends seemed to be similar across the cohorts.

Depression was not reevaluated over time. All of the studies in this review measured depression at one point in time, but depressive symptoms have a tendency to vary over the life-course. Previous papers have described the difference between a single transient episode of depressive symptoms and recurrent depressive symptoms.[19, 20] The findings revealed that a history of recurrent depressive events, but not a history with a single depressive event, were

associated with plaque in the carotid artery and coronary artery calcification.[19] Addressing frequency or duration of depressive episodes could influence the findings of studies within this literature review.

1.2 HIV INFECTION

According to the Centers for Disease Control and Prevention, over 1.1 million adults are living with HIV infection in the United States.[21] Adults with HIV infection (HIV+) are now aging successfully due to effective clinical management and antiretroviral therapy (ART).[22, 23] The risk of chronic disease, however, is greater among HIV+ adults compared to individuals without HIV (HIV-).[24] Heart failure (HF) is a chronic cardiovascular disease that poses a 20% lifetime risk in Americans over age 40, and the risk is substantially higher in HIV+ adults.[25-27]

HIV infection is independently associated with CVD. This association has been repeatedly reported for CVD events, such as acute myocardial infarction (AMI), heart failure, and stroke.[25, 28, 29] Subclinical CVD measures also tend to indicate a greater burden of early cardiovascular disease in HIV-infected persons compared to healthy comparators. For example, studies show thicker intima-media thickness (IMT), greater coronary artery calcification (CAC), faster pulse-wave velocity (PWV), and endothelial dysfunction with HIV infection.[30] Adiposity stores are also abnormal with HIV. Potential mechanisms for the elevated risk of cardiovascular disease include direct damage to the arterial wall from the HIV viral particles, arterial damage due to chronic inflammation, absence of repair due to loss of CD4+ cells, or secondary effects due to highly active antiretroviral therapy (HAART)-induced metabolic syndrome.[31]

1.2.1 Pathophysiological mechanisms

Antiretroviral therapy-related metabolic disorder Evidence exists that the protease inhibitor class of antiretroviral therapy drugs is associated with cardiovascular disease that results from lipid dysfunction.[26] However, a recent study found that this association is not significant across the whole class of protease inhibitors. Monforte *et al.* determined that the protease inhibitor atazanavir was not significantly associated with cardiovascular or cerebrovascular disease events.[32]

HIV exposure to vasculature Early in the HIV epidemic, before effective therapy existed to suppress the viral load and slow the progression to AIDS, clinicians were noticing increased rates of myocarditis and opportunistic infections, which quickly resulted in heart failure and death.[26, 33-35]

Chronic inflammation and inflammaging HIV is associated with ongoing inflammation. Monocytes and macrophages remain activated and produce high levels of CRP, TNF-alpha, IL-6, and soluble CD14. [32] Chronic inflammation is damaging to the vascular walls and leads to endothelial dysfunction, which is associated with cardiovascular disease events.

Blood coagulation The HIV infection response is also associated with clotting disorders. [32] As described in the section above, activated platelets produce signals that increase aggregation with other platelets and lead to ischemic events.

1.2.2 HIV infection and heart failure

Studies published during the pre-HAART era (prior to 1996) described heart disease that developed in AIDS patients. With AIDS, these patients developed secondary infections and

myocarditis, which led to HF. Today, the manifestations of CVD have shifted to complications with aging and chronic HF, as previously noted. Seven papers comparing HIV-infected and -uninfected persons in the post-HAART era were included in this review (Table 6-2).

Only two of the seven papers specifically described heart failure incidence as their primary outcome. The remaining five papers described measures of left ventricle (LV) dysfunction using echocardiogram. While LV dysfunction often precedes heart failure, this subclinical measure is not equivalent to a clinical diagnosis of heart failure.[36]

The two studies that reported HF diagnoses were considerably larger than the five imaging studies. The imaging studies ranged in size from 46 to 242 participants, while the HF studies each included more than 8,000 participants. With mean participant ages ranging from 34 to 48 years, the participants were notably younger compared to the articles describing depression and heart failure. One of the studies included only men, while the remaining studies included more than 60% men.

Butt *et al*. published the first paper to identify a significantly higher risk of HF hospitalizations of HIV+ persons compared to HIV- persons in a large cohort study (HR = 1.81; 95% CI, 1.39 – 2.36).[37] This study used ICD-9-CM HF codes from medical records of participants enrolled in two large cohort studies: Veterans Aging Cohort Study Virtual Cohort (VACS-VC) and the 1999 Large Health Study of Veteran Enrollees (LHS). A secondary analysis revealed a significant association between HIV and HF when the baseline HIV-1 RNA concentrations were ≥ 500 copies/mL but not when the viral particles were adequately controlled and below 500 copies/mL.

The other study that compared incident HF in HIV positive and negative individuals further stratified the participants by race.[38] Using the United States National Hospital Discharge

Surveys, Oramasasionwu *et al*. supported the trend found in the VACS-VC/LHS cohorts. The proportion of HF hospitalizations was higher in those with HIV/AIDS compared to those without HIV in both African Americans and whites. Additionally, the proportion of HF hospitalizations in HIV-infected African Americans was significantly higher compared to HIV-infected whites.

There was a common trend in the five studies that described subclinical measures of the heart using echocardiogram images. HIV-infected persons had significantly poorer measures of structure and function compared to those negative for HIV. Notable findings included: increased LV diameter, increased LV mass, decreased wall strain, and decreased LV ejection fraction in the HIV-infected participants.[39-42] To further differentiate whether alterations to the LV were entirely explained by high blood pressure, Grandi *et al*. stratified participants into four groups: HIV-infected hypertensives; HIV-infected normotenstives; HIV-uninfected hypertensives; and HIV-uninfected normotensives. In addition to noting greater LV mass in HIV-infected persons, they also found that HIV-infected normotenstives had significantly greater LV mass compared to HIV-uninfected normotensives. They concluded that HIV itself must contribute to the commonly observed preclinical changes to the heart.

1.3 DEPRESSION AND HIV INFECTION

Depression is common in the US with the general population facing an estimated 6.6% 12-month risk of developing major depressive disorder (MDD).[43] Depression is one of the most common comorbidities of HIV.[44] Estimates for 12-month MDD prevalence among HIV+ adults range from 5% to 10%.[45] A meta-analysis reported that the frequency of MDD diagnoses among HIV+ participants was nearly two times higher than the frequency among HIV- participants.[46] Like

HIV infection, MDD may also increase the risk for HF.[11, 12, 47, 48] The estimates of depression among those with HIV infection vary widely.

1.4 UNANSWERED QUESTIONS

In the literature reviewed above, the risk of incident HF was significantly higher in those defined as having depression in three of the five studies reporting this association. This association was supported by four studies that described biomarkers and subclinical measures of HF. Both studies that investigated the association of incident HF in HIV-infected individuals, reported an increased risk of HF with infection. The remaining five studies reported that HIV is positively associated with both left ventricle mass and left ventricular dysfunction, which are precursors to heart failure.

The underlying processes that link these conditions are not completely understood. Investigators have proposed numerous hypotheses for the pathophysiological mechanisms linking HIV to HF and depression to HF. Interestingly, some of the hypotheses overlap.[3, 49]

Two hypotheses that have been suggested as possible mechanisms for both depression and HIV are systemic inflammation and autonomic nervous system dysfunction.[3, 49] During systemic inflammation, pro-inflammatory cytokines are elevated. The downstream effects of this include endothelial dysfunction and impairment of contractile strength of heart muscle cells. Dysfunction of the autonomic nervous system increases heart rate, induces vasoconstriction, and increases blood pressure. Each of these conditions make the heart work harder, which could lead to HF. Systemic inflammation and the autonomic nervous system are two candidates for further

research in better understanding the physiological mechanisms underlying depression, HIV, and HF.

Although HIV and depression share several physiological pathways that increase the risk of cardiovascular disease, current literature lacks observational studies aiming to determine whether or not these conditions interact to produce excessive cardiovascular disease. This dissertation will investigate cardiovascular disease outcomes and biomarker concentrations to further understand whether HIV and depression interact during the development of cardiovascular disease.

2.0 VETERANS AGING COHORT STUDY

2.1 VACS

The Veterans Aging Cohort Study (VACS) is a large prospective cohort developed to explore the association between HIV, HIV treatment, comorbid conditions, and disease outcomes.[50] Investigators developed an algorithm to identify HIV positive patients using electronic medical records at the Veterans Administration (VA). The algorithm identified 47,805 HIV+ Veterans within 4.1 million records from the VA system between 1998 and 2004 (Figure 2-1). The Immunology Case Registry, which documents HIV patients in the VA, was used as the gold standard for calculating the positive predictive value (88%). Each HIV+ Veterans identified by the algorithm was matched to two HIV negative comparators who were similar in age, sex, race/ethnicity, geographical location, and year identified. The Virtual Cohort dataset includes administrative and clinical data, diagnostic and procedure code data, healthcare utilization data, and outpatient pharmacy data. Since the VA is the largest provider for HIV patients in the United States, epidemiological findings within the cohort will have significant implications to managing healthcare procedures and addressing healthcare costs.

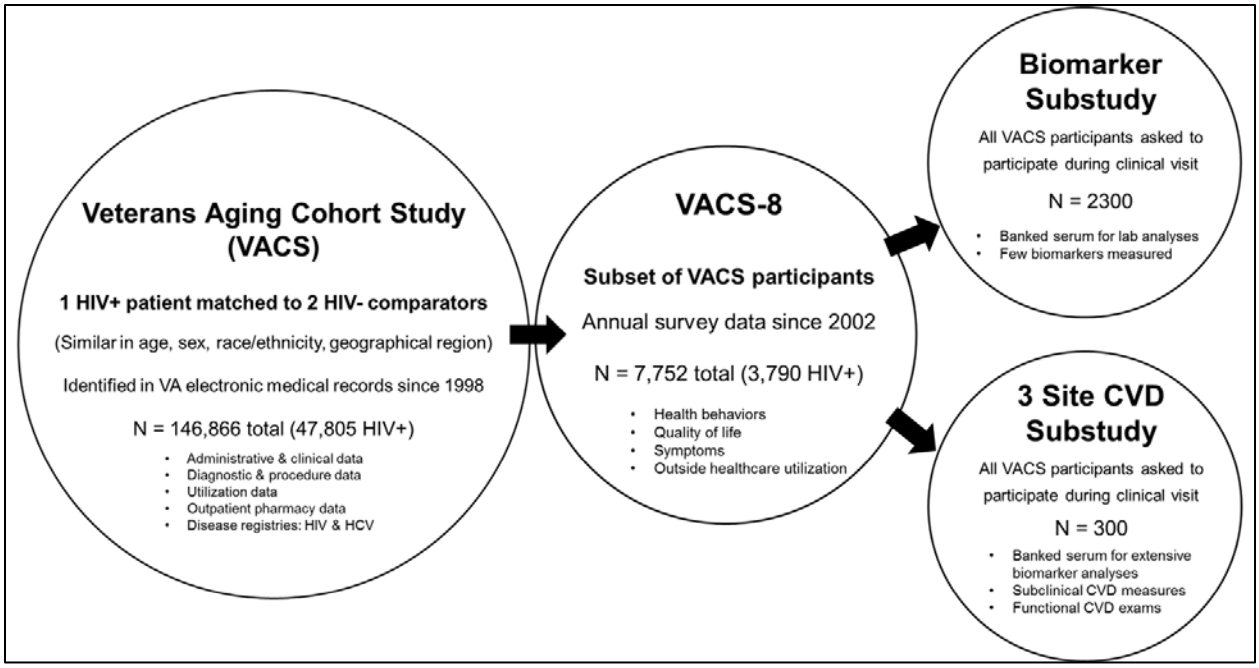

Figure 2-1 Veterans Aging Cohort Study (VACS) participants and data

2.2 VETERANS AND DEPRESSION

Depression is common in the VA health care system. According to a fact sheet provided by the *National Alliance on Mental Illness*, 14% of veterans entering the VA from 2000 – 2007 had a diagnosis of depression in their VA medical record.[51] Similarly, the RAND Corporation surveyed a sample of veterans from Operations Enduring Freedom and Iraqi Freedom in Afghanistan and Iraq (N = 1,965) using the Patient Health Questionnaire-8 (PHQ-8) and found that 14% had symptoms of major depression.[52]

The current VA website for depression refers veterans to their primary care physician for an initial evaluation of depressive symptoms and a prescription for antidepressant medication.[53] Mental health professionals (psychiatrists, psychologists, social workers, licensed professional counselors, and psychiatric nurses) are recommended if the pharmacological treatments do not

relieve symptoms. The VA provides two evidence-based, non-pharmacological options for depression: Cognitive Behavioral Therapy and Acceptance and Commitment Therapy. According to the RAND report, just over half of the veterans meeting criteria for post-traumatic stress disorder and depression sought professional treatment for their symptoms in the previous year, which was similar to the rate for seeking treatment in civilians.[52]

3.0 DEPRESSION AND HIV INFECTION ARE RISK FACTORS FOR HEART FAILURE AMONG VETERANS: VETERANS AGING COHORT STUDY

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3.1 ABSTRACT

BACKGROUND: Both HIV and depression are associated with increased heart failure (HF) risk. Depression, a common comorbidity, may further increase the risk of HF among HIV+ adults. We assessed the association of HIV and depression with incident HF risk.

METHODS AND RESULTS: Veterans Aging Cohort Study (VACS) participants free from cardiovascular disease at baseline (N = 81,427; 26,908 HIV+, 54,519 HIV-) were categorized into four groups: HIV- without major depressive disorder (MDD) [reference]; HIV- with MDD; HIV+ without MDD; and HIV+ with MDD. ICD-9 codes from medical records were used to determine MDD and the primary outcome, HF. After 5.8 follow-up years, HF rates per 1000 person-years were highest among HIV+ participants with MDD (9.32; 95% CI, 8.20-10.6). In Cox proportional hazards models, HIV+ participants with MDD had significantly higher risk of HF [adjusted hazard ratio (aHR) = 1.68; 95% CI, 1.45-1.95] compared to HIV- participants without MDD. MDD was associated with HF in separate fully adjusted models for HIV- and HIV+ participants (aHR = 1.21; 1.06-1.37 and 1.29; 1.11-1.51, respectively). Among those with MDD, baseline antidepressant use was associated with lower risk of incident HF events (aHR = 0.76; 0.58-0.99).

CONCLUSIONS: Our study is the first to suggest MDD is an independent risk factor for HF in HIV+ adults. These results reinforce the importance of identifying and managing MDD among HIV+ patients. Future studies must clarify mechanisms linking HIV, MDD, antidepressants, and HF; and identify interventions to reduce HF morbidity and mortality in those with both HIV and MDD.

3.2 INTRODUCTION

Antiretroviral therapy (ART) and effective clinical management have resulted in improved life expectancy for adults with HIV infection (HIV+).[22, 23] Yet, the risk for cardiovascular disease (CVD) is higher for HIV+ adults compared to those without HIV (HIV-).[24] The risk of heart failure (HF), for example, is significantly higher in HIV+ adults compared to HIV- adults who are similar in age, gender, and race/ethnicity (adjusted HR = 1.81; 95% CI, 1.39 – 2.36, in a cohort of veterans).[25, 26, 54]

Poor mental health is an additional concern for HIV+ adults. Depression is common in the US with the general population facing an estimated 6.6% 12-month risk of developing major depressive disorder (MDD).[43] Estimates for 12-month MDD prevalence among HIV+ adults range from 5% to 10%.[45] A meta-analysis reported that the frequency of MDD diagnoses among HIV+ participants was nearly two times higher than the frequency among HIV- participants.[46] Like HIV infection, MDD may also increase the risk for HF.[11, 12, 47, 48]

Possible mechanisms for the association between HIV and HF include chronic inflammation and platelet activation.[26] Similarly, depression is associated with autonomic nervous system dysregulation, inflammation, and platelet activation.[7, 55, 56] It stands to reason that HIV+ adults with MDD may be at heightened risk for HF compared to the remaining population; however, to date, no studies have examined the risk of HF in individuals burdened with co-occurring HIV and MDD.

We investigated the association between HIV, MDD, and incident HF among a subset of HIV+ and HIV- veterans from the Veterans Aging Cohort Study (VACS). We hypothesized that HIV+ participants with MDD would have a significantly higher risk of incident HF than participants with only one or neither of these conditions after adjusting for cardiovascular risk

factors. In addition, we explored the effects of antidepressant use, HIV severity, and ART use on this association.

3.3 METHODS

Participants

Details of the prospective, longitudinal Veterans Aging Cohort Study (VACS) have been published previously.[50] Since 1998, the VACS continually enrolled HIV+ and age-, sex-, race/ethnicity-, and geographic region-matched HIV- veterans in the same calendar year from the US Department of Veterans Affairs (VA) system. For this analysis, data from VACS participants alive and enrolled as of April 1, 2003 were extracted from the VA national electronic medical record system. The institutional review boards from the University of Pittsburgh, Yale University, and West Haven VA Medical Center approved this study.

Participants were included in this analysis if they were free of clinical CVD at baseline (April 1, 2003). Prevalent CVD at baseline was defined using International Classification of Diseases, Ninth Revision (ICD-9) codes for HF, acute myocardial infarction, unstable angina, stroke or transient ischemic attack, peripheral vascular disease, or cardiovascular revascularization on or before their baseline date. The final sample included 81,427 Veterans (26,908 HIV+, 54,519 HIV-).

Independent Variables

We categorized participants into four groups: HIV- without MDD (reference); HIV- with MDD; HIV+ without MDD; and HIV+ with MDD. Participants were considered HIV+ if they had at least one inpatient and/or two or more outpatient ICD-9 codes for HIV at baseline. The

algorithm used to identify HIV+ veterans has high sensitivity (90%), specificity (99.9%), and positive predictive value (88%).[50]

Participants were considered to have MDD if at least one ICD-9 code for MDD (296.2x and 296.3x) was ever in their VA medical record prior to the baseline visit. In a small study that compared MDD diagnoses made by general practitioners in primary care settings compared to Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV) criteria ranges for MDD, specificity was 89% while sensitivity was 79%.[57] These findings were supported by a larger study that investigated the validity of billing diagnoses for clinical depression in electronic medical records.[58]

Dependent Variables

The primary outcome for this report, HF, was determined using VA and Medicare ICD-9 codes (428.xx, 429.3, 402.11, 402.91, 425.x), a method shown to have a positive predictive value of 94.3%.[59] The follow-up time for participants began from their first clinical encounter on or after 4/1/2003 and continued until a HF event, death, or the last date of follow-up (12/31/2009). **Figure 3-1** illustrates the timeline of independent and dependent variables.

Covariates

Administrative data were used to obtain age, sex, and race/ethnicity. Outpatient and laboratory reports from baseline visits stored in the VA medical record provided data regarding hypertension, diabetes mellitus, lipid concentrations, hemoglobin concentrations, renal function, atrial fibrillation, atrial flutter, alcohol abuse or dependence, cocaine abuse or dependence, and hepatitis C virus (HCV) infection. Baseline body mass index (BMI; kg/m^2) and smoking status were acquired from health factor data collected by the VA and recorded in the VA medical

record. Baseline antidepressant and HMG CoA reductase inhibitor (statin) data were obtained from VA pharmacy records.[50]

Three hypertension categories were used: none (blood pressure <140/90 mmHg and no antihypertensive medication use); controlled (blood pressure <140/90 mmHg and antihypertensive medication use); and uncontrolled (blood pressure ≥140/90 mmHg).[60] Diabetes mellitus diagnosis was determined using a combination of glucose levels, anti-diabetes medication, and ICD-9 codes; an algorithm previously validated in the VACS.[61] Dyslipidemia was assessed using levels of low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), and triglycerides measured in mg/dL. Statin use was determined within six months from enrollment. Anemia was based on hemoglobin concentrations (g/dL), and renal function was based on estimated glomerular filtration rate (eGFR; mL/min/1.73 m^3). Alcohol abuse or dependence and cocaine abuse or dependence were measured based on ICD-9 codes.[62] Hepatitis C virus infection was defined by one or more inpatient and/or two or more outpatient ICD-9 codes for a positive HCV antibody test result.[63] Body mass index and smoking status (current, past, and never) were included in the VA electronic medical health record following prompts to the clinicians during patient visits. Obesity was defined as BMI $\geq$ 30 kg/m^2. The smoking status reported in this health factor dataset has shown high agreement with self-reported smoking status on VACS-8 surveys.[64]

Antidepressant use was defined as documentation of a filled prescription for selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), or other antidepressant use from the VA pharmacy records during the baseline period (1998-2003). Medications were classified as "other" if they were in the following classes: tetracyclic antidepressant, monoamine oxidase inhibitor, serotonin-norepinephrine reuptake inhibitor, serotonin antagonist and reuptake

inhibitor, norepinephrine reuptake inhibitor, norepinephrine-dopamine reuptake inhibitor, and miscellaneous (**Supplemental Table, Table 3-5**). Generic and brand names for antidepressants were used to search outpatient pharmacy records.

We included HIV-specific variables (CD4+ T-cell (CD4) counts, HIV-1 RNA, and ART use) for HIV+ participants from two time periods: baseline and recent.[28] Baseline variables were obtained during participant visits within 180 days of the baseline enrollment date (4/1/2003). Recent variables were obtained during the visit closest to HF, death, or the last follow-up date (12/31/2009). Antiretroviral medications were based on pharmacy data and categorized by drug class [i.e., nucleoside reverse-transcriptase inhibitors (NRTI), nonnucleoside reverse-transcriptase inhibitors (NNRTI), or protease inhibitors (PI)]. Additionally, four types of ART regimens were defined: NRTI with PI; NRTI with NNRTI; other regimen; and no ART use (reference). A previous study reported that 96% of HIV+ veterans obtain their ART medications through the VA system.[50]

Statistical analysis

Baseline descriptive statistics were calculated for each HIV/MDD group. T-tests (or non-parametric counterpart) and chi-square tests were used to determine significant differences between the groups as appropriate. Incident HF diagnosis rates per 1000 person-years were calculated for each HIV/MDD group. Cox proportional hazards regression was used to model the association between HIV/MDD group and incident HF, adjusting for age, sex, race/ethnicity, BMI, hypertension, diabetes mellitus, LDL-c, HDL-c, triglycerides, statin use, hemoglobin, renal function, atrial fibrillation, atrial flutter, smoking status, alcohol abuse or dependence, cocaine abuse or dependence, and HCV infection. A Kaplan-Meier curve was created to display time to incident HF by the four HIV/MDD groups. Among those with MDD, HF incidence rates per

1000 person-years and adjusted hazard ratios were calculated by HIV status and antidepressant use. In a second analysis, we used Cox regression to model the association of MDD and incident HF among the HIV+ participants. This analysis included additional adjustments for baseline and recent CD4 counts, HIV-1 RNA, and ART use. We included only participants with a diagnosis of MDD in our third analysis which explored the association between antidepressant use and incident HF among HIV+ and HIV- participants.

3.4 RESULTS

Within this cohort of 81,427 veterans, MDD prevalence was 17.0% overall and not significantly different between HIV+ and HIV- participants (18.8% vs. 16.1%, respectively). The four HIV/MDD groups made up the following proportions of the total sample: HIV- without MDD, 56.2%; HIV- with MDD, 10.8%; HIV+ without MDD, 26.8%; and HIV+ with MDD, 6.2%.

Baseline characteristics differed between the four HIV/MDD groups (**Table 3-1**). Regardless of MDD diagnosis, HIV+ participants were more likely than HIV- participants to have low HDL-c, high triglycerides, HCV infection, renal disease, anemia, and cocaine abuse or dependence and to be current smokers. However, HIV+ participants were less likely to have hypertension, diabetes, and high LDL-c and to be obese. Regardless of HIV status, participants with MDD were more likely than participants without MDD to have diabetes, high triglycerides, HCV infection, cocaine abuse or dependence, and alcohol abuse or dependence; to be current smokers; and to use antidepressant medications (all with $p < 0.05$).

During a median of 5.8 (IQR, 3.3 – 6.6) years of follow-up, there were 2666 incident HF events. The HF rate per 1000 person-years was significantly higher among HIV+ participants

with co-occurring MDD compared to rates in the other three groups, i.e. HIV- without MDD, HIV- with MDD, and HIV+ without MDD (**Table 3-2**).

After adjusting for traditional CVD risk factors, HIV- participants with MDD, HIV+ participants without MDD, and HIV+ participants with MDD had higher risk of incident HF than HIV- participants without MDD (**Table 3-3**). Age, hypertension, diabetes, low hemoglobin, low eGFR, atrial fibrillation, current smoking, cocaine abuse or dependence and HCV infection were independently associated with increased risk of incident HF. Hispanic race/ethnicity was associated with a lower risk of incident HF. When this model was additionally adjusted for SSRI, TCA, and other antidepressant use, the risk of HF remained elevated among HIV- participants with MDD (adjusted HF (aHR) = 1.17; 95% CI, 1.02 – 1.34), HIV+ participants without MDD (1.28; 1.16 – 1.41), and HIV+ participants with MDD (1.64; 1.41 – 1.92) compared to the referent group. Participants with co-occurring HIV infection and MDD diagnosis had the poorest survival free of HF of all four groups (**Figure 3-2**). In an exploratory analysis, we found that the multiplicative interaction between HIV and MDD was not significant ($p = 0.32$).

We further explored incident HF risk in HIV- and HIV+ participants separately. MDD was associated with increased risk of HF in both groups (aHR = 1.21; 95% CI, 1.06 – 1.37 and 1.29; 1.11 – 1.51, respectively). Among HIV+ participants, MDD remained a significant risk factor for HF after further adjusting for baseline CD4 count, baseline HIV-1 RNA concentration, and ART regimen documented at the baseline visit (aHR = 1.30, 95% CI, 1.11 – 1.51). We found similar results when the model included baseline PI, NRTI, and NRTI use; recent CD4 count, HIV-1 RNA concentration and ART regimen; or recent PI, NRTI, and NRTI use.

The majority of participants with MDD had at least one antidepressant prescription during the baseline period (90.2%). Among all participants in the sample with MDD, baseline antidepressant use was associated with fewer incident HF events, adjusting for HIV and cardiovascular disease risk factors (aHR = 0.76; 95% CI, 0.58 – 0.99). In a model that stratified the MDD participants by both HIV status and antidepressant use, the rates of incident HF were highest among HIV+ participants who did not use antidepressants (**Table 3-4**).

3.5 DISCUSSION

Our findings indicate that both depression and HIV are associated with an increased risk of HF in veterans, even after adjusting for traditional CVD risk factors, comorbidities, and substance use. Participants with co-occurring HIV and MDD had the highest rates and risk of HF relative to those with only one of the conditions or neither condition. Furthermore, among HIV+ veterans, depression was associated with an increased risk of HF after additional adjustment for CD4 cell count, HIV-1 RNA levels, and ART use.

Our findings are consistent with previous studies reporting associations between (a) HIV and incident HF and (b) depression and incident HF in HIV- samples.[25-27, 48] However, this study is the first to simultaneously examine HIV status, MDD diagnosis, and antidepressant use as predictors of incident HF in a large national cohort of HIV infected and uninfected people. In addition, our results are the first to suggest that MDD is an independent risk factor for HF in HIV+ adults.

The physiological mechanisms underlying the associations of HIV infection and depression with future HF have yet to be elucidated. With HIV infection, the risk of HF may be

explained by vascular damage associated with the virus itself, chronic inflammation, lack of vascular repair due to CD4 cell depletion, or dyslipidemia following HIV infection or ART-induced metabolic syndrome.[25, 28, 31, 65, 66] With depression, possible mechanisms include alterations to the hypothalamic-pituitary-adrenal axis, dysregulation of the autonomic nervous system, chronic inflammation, and platelet activation.[67, 68] In addition to these physiological changes, both HIV infection and depression are associated with unhealthy behavioral changes, such as substance use and decreased physical activity, which are risk factors for HF.[3, 69]

In this study, HIV+ participants with co-occurring MDD had the highest risk of HF. The Infectious Diseases Society of America has stressed the importance of recognizing depression in HIV+ patients.[70] Our findings bolster this recommendation by adding another reason for doing so – i.e., depression as a potential risk factor for HF. In Table 3-4, we report preliminary evidence that raises the possibility that antidepressant use may decrease the excess risk for HF in HIV+ and HIV- adults. However, a prospective randomized controlled trial is needed to determine whether depression is a causal risk factor for HF and whether depression interventions reduce the risk of HF in the HIV infected and uninfected populations.[2, 71]

There are limitations of this study that warrant discussion. First, as our participants were predominantly men, the findings might not generalize to women. Second, HF and depression were based on ICD-9 codes. Therefore, some misclassification may have occurred (e.g., patients with true MDD or HF was not indicated in their medical record with an ICD-9 code), however, such misclassification would have biased our results to the null. Moreover, previous studies have shown that the ICD-9 codes for HF and MDD are highly correlated with clinical outcomes.[57, 59] Third, baseline depressive disorder diagnosis was used as a predictor. Depressive symptom severity tends to fluctuate over time, and previous findings suggest that the mean of

symptom severity assessed at multiple time points is a stronger predictor of subclinical CVD than depressive symptom severity assessed at one time point.[20] However, because depressive episodes are likely to recur in those with a MDD diagnosis, a baseline measure of MDD diagnosis should capture those at risk for chronic exposure to the unhealthy impact of depression.[72, 73] Lastly, our findings that depression treatment is associated with a reduced risk of HF among HIV infected veterans with MDD, while novel and intriguing, should be interpreted with caution. As this is an observational study and not a randomized control trial, we cannot eliminate confounding due to indication associated with the treatment of depression. Moreover, improved HF outcomes may be attributed to more frequent visits with a provider and better management of CVD risk factors and other medical conditions in addition to MDD treatment. Additionally, only 10% of participants with an MDD diagnosis did not have a prescription for an antidepressant during the baseline period. The high prevalence of treatment is likely a reflection of the fact that MDD in our study was determined by clinical diagnostic codes and not by a formal depression screening instrument administered to all participants. It is likely that some participants with unrecognized depression existed in our no MDD group. This possible misclassification, however, would lead us to underestimate the strength of the MDD-HF relationship, as veterans with unrecognized depression would be included in our referent group.

In conclusion, HIV and MDD are each associated with an increased risk of incident HF. HIV infected Veterans with MDD had the highest rates of and risk for HF as compared to Veterans with either HIV, depression, or neither condition. These results suggest that MDD is a possible independent risk factor for HF among HIV+ patients and thus reinforce the importance of screening for and effectively managing depression in this patient population. Future studies in both HIV infected and uninfected adults should aim (a) to clarify the mechanisms underlying the

depression-HF association and (b) to determine whether evidence-based depression treatment may help to reduce HF morbidity and mortality in these populations.

3.6 TABLES AND FIGURES

Table 3-1 Baseline participant characteristics by HIV status and major depressive disorder (MDD) diagnosis (N = 81,427)*

	HIV-uninfected		**HIV-infected**	
Characteristic	**No MDD (*n* = 45,728)**	**MDD (*n* = 8,791)**	**No MDD (*n* = 21,850)**	**MDD (*n* = 5,058)**
Age, years, mean (SD)	48.8 (9.5)	48.1 (7.4)	48.3 (9.7)	47.4 (7.9)
Male, %	97.5	95.6	97.7	95.3
Race / Ethnicity, %				
White	37.0	41.6	37.0	42.5
African American	48.0	46.8	48.5	45.9
Hispanic	7.5	9.2	6.9	8.2
Other	7.4	2.4	7.7	3.4
Body Mass Index $\geq$ 30 kg/m^2, %	38.7	38.6	13.7	16.6
Hypertension, %				
None	58.3	60.8	67.3	68.6
Controlled	9.4	10.1	7.0	7.9
Uncontrolled	32.4	29.0	25.7	23.6
Diabetes mellitus, %	20.0	23.1	13.3	16.1
Lipids, mg/dL, %				
LDL cholesterol < 100	31.2	33.5	46.2	46.5
LDL cholesterol 100 - 129	33.3	33.4	29.7	29.6

Table 3-1 Continued

	HIV-uninfected		HIV-infected	
Characteristic	**No MDD (*n* = 45,728)**	**MDD (*n* = 8,791)**	**No MDD (*n* = 21,850)**	**MDD (*n* = 5,058)**
LDL cholesterol 130 - 159	23.2	21.1	15.9	15.7
LDL cholesterol ≥ 160	12.3	12.0	8.2	8.1
HDL cholesterol ≥ 60	15.0	13.4	11.1	10.2
HDL cholesterol 40 - 59	47.7	45.5	38.0	37.2
HDL cholesterol < 40	37.3	41.1	50.9	52.6
Triglycerides ≥ 150	37.4	42.2	46.9	49.1
Statin use within 6 months of enrollment, %	9.4	11.6	6.4	6.8
Hemoglobin, g/dL, %				
≥ 14	73.1	70.9	55.1	57.1
12 - 13.9	22.9	24.9	31.9	32.0
10 - 11.9	3.2	3.5	9.5	8.5
< 10	0.8	0.8	3.5	2.5
Renal function, mL/min/1.73 m^3, %				
eGFR ≥ 60	95.3	95.9	93.6	94.6
eGFR 30 - 59	4.2	3.7	5.2	4.4
eGFR < 30	0.5	0.3	1.2	1.1
Atrial fibrillation, %	1.0	0.8	0.8	0.7
Atrial flutter, %	0.3	0.4	0.3	0.2
Smoking, %				

Table 3-1 Continued

	HIV-uninfected		HIV-infected	
Characteristic	**No MDD (*n* = 45,728)**	**MDD (*n* = 8,791)**	**No MDD (*n* = 21,850)**	**MDD (*n* = 5,058)**
Never	31.4	22.8	28.4	19.3
Past	16.5	13.4	13.7	11.0
Current	52.1	63.8	57.8	69.7
Alcohol abuse or dependence, %	10.5	27.5	10.8	28.1
Cocaine abuse or dependence, %	5.5	16.3	8.5	23.3
HCV infection, %	13.9	24.0	32.7	43.2
Antidepressant use, %				
SSRI	20.4	73.7	22.8	73.6
TCA	11.3	25.3	14.7	29.2
Other antidepressants†	20.6	70.4	22.2	68.2
HIV-specific risk factors				
CD4 cell count, mm^3, %				
≥ 500 at baseline	…	…	31.4	34.6
200 – 499 at baseline	…	…	40.0	40.5
< 200 at baseline	…	…	28.6	24.9
≥ 500 at recent visit	…	…	41.5	41.7
200 – 499 at recent visit	…	…	39.2	38.4
< 200 at recent visit	…	…	19.3	20.0
HIV-1 RNA, ≥ 500 copies/mL at baseline, %	…	…	55.1	56.5

Table 3-1 Continued

	HIV-uninfected		HIV-infected	
Characteristic	**No MDD (*n* = 45,728)**	**MDD (*n* = 8,791)**	**No MDD (*n* = 21,850)**	**MDD (*n* = 5,058)**
HIV-1 RNA, ≥ 500 copies/mL at recent visit, %	…	…	24.5	26.4
ART use, %				
NRTI at baseline	…	…	48.3	49.6
NNRTI at baseline	…	…	22.6	22.1
PI at baseline	…	…	25.3	27.1
NRTI at recent visit	…	…	73.7	68.1
NNRTI at recent visit	…	…		
PI at recent visit	…	…	38.1	39.8
Regimen, %				
NRTI + PI at baseline	…	…	20.4	21.6
NRTI + NNRTI at baseline	…	…	22.1	21.6
Other at baseline	…	…	6.7	7.2
No ART at baseline	…	…	50.9	49.6
NRTI + PI at recent visit	…	…	32.4	34.1
NRTI + NNRTI at recent visit	…	…	35.9	28.6
Other at recent visit	…	…	8.3	8.6
No ART at recent visit	…	…	23.4	28.8

Abbreviations: ART, antiretroviral therapy; BMI, body mass index (calculated as kg/m^2); eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV,

human immunodeficiency virus; LDL, low-density lipoprotein; MDD, major depressive disorder; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants

*All characteristics were significantly different between groups ($p < 0.05$) except atrial flutter ($p = 0.201$), recent CD4 cell counts ($p = 0.492$), baseline HIV-1 RNA concentration ($p = 0.104$), baseline NRTI use ($p = 0.093$), baseline NNRTI use ($p = 0.436$), and baseline ART regimens ($p = 0.080$)

† See Supplemental Table for medications included in each antidepressant medication category

Table 3-2 Unadjusted rates of incident heart failure by major depressive disorder (MDD) diagnosis and HIV status (N = 81,427)

HIV status / MDD diagnosis	Number of participants	Number of HF events	Rates of HF per 1000 p-y (95% CI)
HIV -- | No MDD	45,728	1,339	6.04 (5.73 – 6.38)
HIV -- | MDD	8,791	319	6.87 (6.16 – 7.67)
HIV + | No MDD	21,850	774	7.56 (7.05 – 8.11)
HIV + | MDD	5,058	234	9.32 (8.20 – 10.60)

Abbreviations: HF, heart failure; HIV, human immunodeficiency virus; MDD, major depressive disorder; p-y, person-years

Table 3-3 Cox proportional hazard regression models examining the association between HIV/MDD group and incident heart failure

Characteristic	HR (95% CI)
HIV / MDD Group	
HIV -- | No MDD	1 [Reference]
HIV -- | MDD	1.19 (1.05 - 1.35)
HIV + | No MDD	1.28 (1.16 - 1.41)
HIV + | MDD	1.68 (1.45 - 1.95)
Age, 10 year intervals	1.78 (1.70 - 1.86)
Female sex	1.01 (0.77 - 1.33)
Race / Ethnicity	
White	1 [Reference]
African American	1.05 (0.96 - 1.15)
Hispanic	0.77 (0.65 - 0.92)
Other	0.92 (0.76 - 1.11)
Body Mass Index ≥ 30	1.25 (1.14 - 1.36)
Hypertension	
None	1 [Reference]
Controlled	1.78 (1.58 - 2.01)
Uncontrolled	1.94 (1.77 - 2.12)
Diabetes mellitus	1.75 (1.61 - 1.91)
Lipids, mg/dL	
LDL cholesterol < 100	1 [Reference]

Table 3-3 Continued

LDL cholesterol 100 - 129	0.88 (0.79 - 0.98)
LDL cholesterol 130 - 159	0.88 (0.78 - 1.00)
LDL cholesterol ≥ 160	0.93 (0.78 - 1.12)
HDL cholesterol ≥ 60	1 [Reference]
HDL cholesterol 40 - 59	1.04 (0.90 - 1.21)
HDL cholesterol < 40	1.04 (0.89 - 1.21)
Triglycerides ≥ 150	1.00 (0.91 - 1.10)
Statin use within 6 months	1.08 (0.97 - 1.21)
Hemoglobin, g/dL	
≥ 14	1 [Reference]
12 - 13.9	1.32 (1.20 - 1.45)
10 - 11.9	1.84 (1.58 - 2.14)
< 10	2.23 (1.75 - 2.85)
Renal function, mL/min/1.73 m^3	
eGFR ≥ 60	1 [Reference]
eGFR 30 - 59	2.01 (1.78 - 2.28)
eGFR < 30	5.21 (4.31 - 6.30)
Atrial fibrillation	2.15 (1.63 - 2.84)
Atrial flutter	1.59 (0.91 - 2.78)
Smoking	
Never	1 [Reference]
Past	1.09 (0.96 - 1.23)
Current	1.42 (1.29 - 1.57)

Table 3-3 Continued

Alcohol abuse or dependence	0.98 (0.86 - 1.12)
Cocaine abuse or dependence	1.27 (1.09 - 1.48)
HCV infection	1.30 (1.19 - 1.43)

Abbreviations: BMI, body mass index (calculated as kg/m^2); eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HR, hazard ratio; LDL, low-density lipoprotein; MDD, major depressive disorder

Table 3-4 Rates and adjusted hazard ratios of incident heart failure among those with baseline MDD (N = 13,849) stratified by HIV and baseline antidepressant use

HIV status	Anti-depressant use	N	HF events	HF rates per 1000 p-y (95% CI)	P value	aHR* (95% CI)	P value
HIV --	Yes	7916	283	6.73 (5.99 – 7.56)	0.25†	1.00 [Reference]	0.28‡
HIV --	No	875	36	8.25 (5.95 – 11.44)		1.21 (0.85 – 1.71)	
HIV +	Yes	4582	206	8.97 (7.82 – 10.28)	0.055§	1.39 (1.14 – 1.68)	0.053‖
HIV +	No	476	28	13.20 (9.11 – 19.11)		2.07 (1.39 – 3.08)	

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HF, heart failure; HIV, human immunodeficiency virus; p-y, person-years

*All models for HF were adjusted for age, sex, race/ethnicity, body mass index, hypertension, diabetes mellitus, lipids, statin use, hemoglobin, renal function, atrial fibrillation, atrial flutter, smoking, alcohol abuse or dependence, cocaine abuse or dependence, and HCV infection

† P value for the comparison of HF rates; HIV- participants who did not use antidepressants at baseline compared to HIV- antidepressant users

‡ P value for the comparison of aHRs; HIV- participants who did not use antidepressants at baseline compared to HIV- antidepressant users

§ P value for the comparison of HF rates; HIV+ participants who did not use antidepressants at baseline compared to HIV+ antidepressant users

‖ P value for the comparison of aHRs; HIV+ participants who did not use antidepressants at baseline compared to HIV+ antidepressant users

Table 3-5 Supplemental Table. List of antidepressants included in study by class*

Class	Generic Name	Brand Name
Selective Serotonin Reuptake Inhibitors (SSRI)	Citalopram	Celexa
	Escitalopram	Lexapro, Cipralex
	Fluoxetine	Prozac, Sarafem
	Fluvoxamine	Luvox
	Paroxetine	Paxil
	Sertraline	Zoloft
Tricyclic Antidepressants (TCA)	Amitriptyline	Elavil, Endep, Levate
	Clomipramine	Anafranil
	Desipramine	Norpramin, Pertofrane
	Dosulepin	Dothiepin, Prothiaden
	Doxepin	Adapin, Sinequan
	Imipramine	Tofranil
	Lofepramine	Feprapax, Gamanil
	Nortriptyline	Pamelor
	Protriptyline	Vivactil
	Trimipramine	Surmontil
Tetracyclic Antidepressant (TeCA)	Amoxapine	Asendin
	Maprotiline	Deprilept, Ludiomil, Psymion
	Mianserin	Bolvidon, Norval, Tolvan
	Mirtazapine	Remeron
Monoamine Oxidase Inhibitors	Isocarboxazid	Marplan

Table 3-5 Continued

(MAOI)	Moclobemide	Manerix
	Phenelzine	Nardil
	Selegiline	L-Deprenyl, Eldepryl, Zelapar, Emsam
	Tranylcypromine	Parnate
	Pirlindole	Pirazidol
Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	Desvenlafaxine	Pristiq
	Duloxetine	Cymbalta
	Milnacipran	Savella
	Venlafaxine	Effexor, Effexor XR
Serotonin Antagonist and Reuptake Inhibitor (SARI)	Etoperidone	Axiomin, Etonin
	Lubazodone	YM-992, YM-35,995
	Nefazodone	Serzone, Nefadar
	Trazodone	Desyrel, Apo-Trazodone
Norepinephrine Reuptake Inhibitor (NRI)	Reboxetine	Edronax , Vestra
	Viloxazine	Vivalan
Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)	Bupropion	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban
	Dexmethylphenidate	Focalin
	Methylphenidate	Ritalin, Concerta
Miscellaneous	Tianeptine	Stablon
	Viloxazine	Vivalan
	Tandospirone	Sediel

Table 3-5 Continued

	Ago melatine	Valdoxan

*Medications were classified as “other” if they were in the following classes: tetracyclic antidepressant, monoamine oxidase inhibitor, serotonin-norepinephrine reuptake inhibitor, serotonin antagonist and reuptake inhibitor, norepinephrine reuptake inhibitor, norepinephrine-dopamine reuptake inhibitor, and miscellaneous

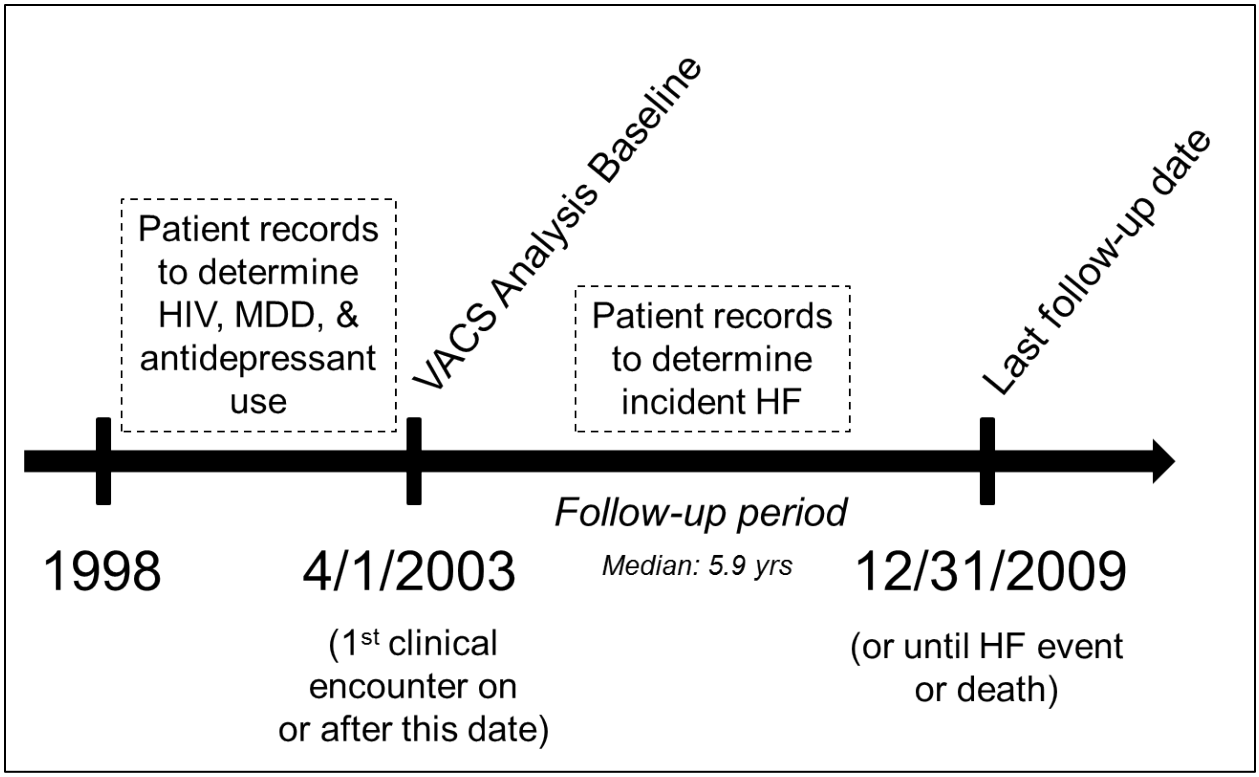

Figure 3-1. Timeline for independent and dependent variables

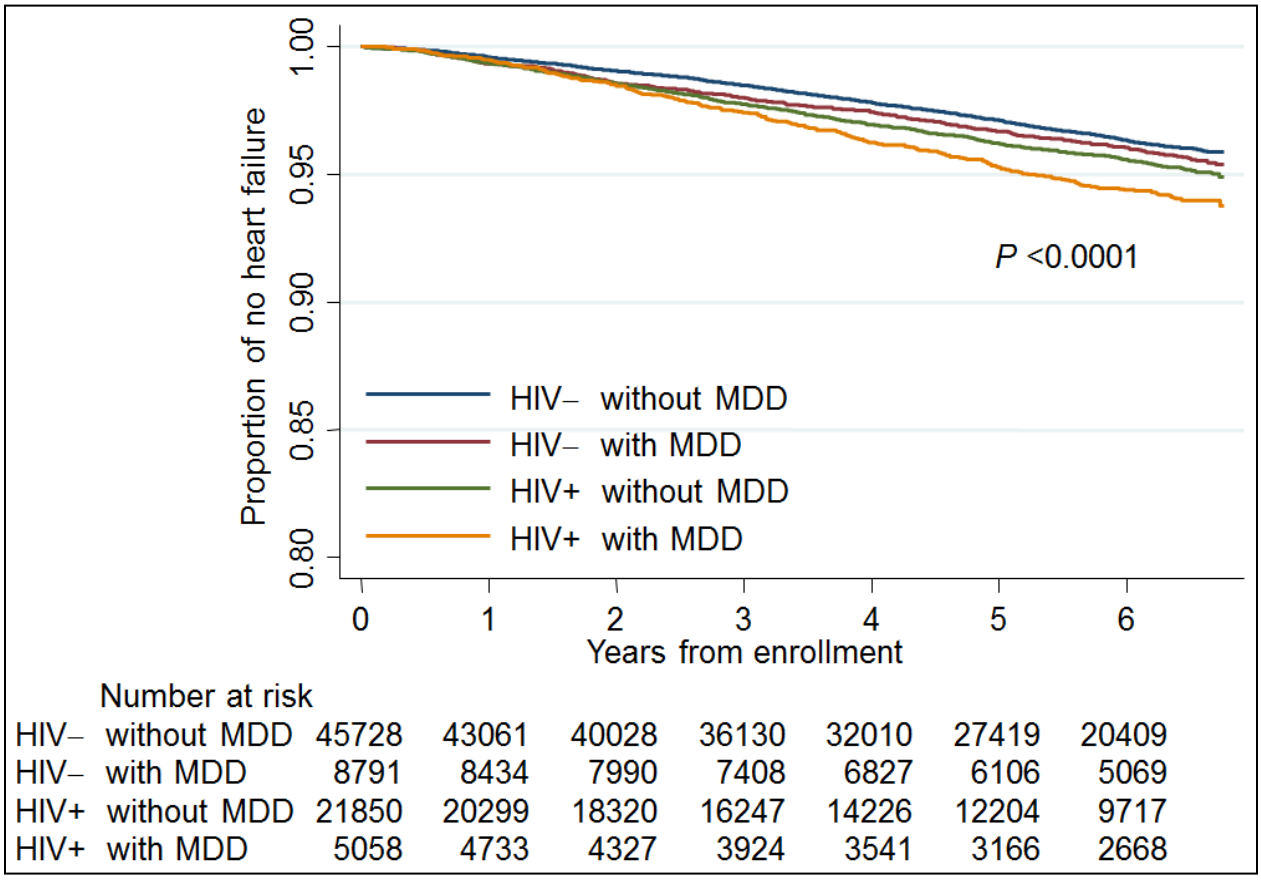

Figure 3-2. Kaplan Meier survival analysis by major depressive disorder (MDD) diagnosis and HIV status (N = 81,427)

4.0 ASSOCIATION BETWEEN DEPRESSION AND BIOMARKERS OF INFLAMMATION, ALTERED COAGULATION, MONOCYTE ACTIVATION, AND METABOLISM IN VETERANS WITH AND WITHOUT HIV INFECTION

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4.1 ABSTRACT

BACKGROUND: Major depressive disorder (MDD) is a risk factor for cardiovascular disease in veterans with and without HIV infection. The mechanism underlying this association is not clear. We hypothesized that markers of inflammation, coagulation, monocyte activation, and metabolism would be positively associated with depression in a cohort of veterans with and without HIV infection.

METHODS: Participants in this study were enrolled in the Veterans Aging Cohort Study (VACS). This large, prospective cohort study included HIV+ and HIV- veterans who were matched on age, sex, race/ethnicity, and geographical region. A subset of these participants, free of cardiovascular disease, were enrolled in the Biomarker Substudy and provided blood for laboratory analysis. Interleukin-6 (IL-6), d-dimer, soluble CD14 (sCD14), glucose, and lipids were quantified. Depression was defined using medical record diagnoses for major depressive disorder (MDD) and self-reported depressive symptoms. Standard multiple regression models provided information about the association between depression, HIV infection, and biomarker concentrations, adjusting for possible confounding variables.

RESULTS: In this sample of 2,099 participants, 678 (32.3%) had a diagnosis of MDD at baseline and 456 (21.7%) participants reported recent symptoms of major depression (Patient Health Questionnaire-9 scores $\geq$ 10). In models adjusted for HIV and other significant covariates, MDD was associated with glucose concentrations in the highest quartile (OR = 1.39; 95% CI, 1.09 – 1.77) and increased concentrations of LDL-c (β = 3.94; 95% CI, 0.43, 7.45), while PHQ-9 scores $\geq$ 10 were associated with higher triglyceride concentrations (β = 0.08; 95%

CI, 0.01 – 0.14). In models restricted by HIV status and adjusted for age, sex, and race/ethnicity, MDD was associated with increased concentrations of IL-6 and sCD14 in the HIV- participants, and associated with increased concentrations of glucose and decreased concentrations of HDL-c in the HIV+ participants.

CONCLUSIONS: In this sample of veterans, we found significant associations between depression and altered concentrations of biomarkers. The changes observed in the HIV- participants were different from the changes observed in the HIV+ participants. These findings suggest that the physiological pathways mediating depression and cardiovascular disease may differ with co-occurring HIV infection. To prevent the risk of cardiovascular disease with depression, interventionists should consider the HIV status of their patients.

4.2 INTRODUCTION

We recently demonstrated that major depressive disorder (MDD) is a risk factor for both incident heart failure and acute myocardial in veterans with and without HIV infection.[74, 75] It is not clear whether depression and HIV infection share physiological mechanisms that drive the elevated risk of cardiovascular disease (CVD).

Clinical depression and depressive symptoms are associated with systemic effects including inflammation, coagulation, monocyte activation, and the metabolic syndrome.[1, 76-79] These pathologies are also seen with HIV infection.[80, 81] Since depression is highly prevalent with HIV infection, it is important to know how the combination of depression and HIV infection affect the body at a physiological level.[44]

The objective of this study was to determine whether depression was associated with biomarkers for inflammation, altered coagulation, monocyte activation, and metabolism in a cohort of veterans with and without HIV infection. Our primary hypothesis was that depression would be associated with significantly higher concentrations of IL-6, d-dimer, soluble CD14, glucose, LDL-c, and triglycerides, and significantly lower concentrations of HDL-c in both HIV- and HIV+ veterans. Second, we hypothesized that co-occurring depression and HIV infection would interact and be associated with a biomarker profile worse than what would be expected if only one of these two conditions were present.

4.3 METHODS

Participants

The Veterans Aging Cohort Study (VACS) is a large, prospective cohort study that continuously enrolled HIV+ veterans from the US Department of Veterans Affairs (VA) system beginning on April 1, 2003.[50] Participants with HIV infection were matched to two HIV-uninfected participants by age, sex, race/ethnicity, and geographical region during the same calendar year. The Biomarker Substudy is a subset of VACS participants who provided a blood sample for analysis of interleukin-6 (IL-6), d-dimer, soluble CD14 (sCD14), and a metabolic panel during a clinical visit between 2005 – 2006.[80]

Participants were excluded from this analysis if they had pre-existing clinical CVD or if they did not complete all nine items on the Patient Health Questionnaire (PHQ-9). Clinical CVD was defined as documentation of International Classification of Diseases, Ninth Revision (ICD-9) codes for acute myocardial infarction, heart failure, unstable angina, stroke or transient

ischemic attack, peripheral vascular disease, or cardiovascular revascularization in the VA medical record. The final sample included 2,099 veterans (1,365 HIV+, 734 HIV-).

Independent Variables

During VACS enrollment, participants were classified as HIV+ if their electronic medical record included at least one inpatient diagnosis for HIV diagnosis or at least two outpatient HIV diagnoses, using ICD-9 codes.[50] HIV status was confirmed with the VA's Immunology Case Registry. This algorithm for HIV status has high sensitivity (90%), specificity (99.9%), and positive predictive value (88%).[50]

The Biomarker Substudy provided two measures of depression: clinical depression diagnosis and self-reported symptoms of major depression. Clinical depression was defined using electronic medical record data. Participants were classified as having major depressive disorder (MDD) if their medical record included at least one ICD-9 code for MDD (296.2x and 296.3x) between 1998 and the first clinical visit on or after April 1, 2003. Depressive symptoms were determined with the nine-item Patient Health Questionnaire (PHQ-9), a self-assessment that measures depressive symptom severity during the two weeks preceding the questionnaire.[82] Cumulative PHQ-9 scores ranging from 0 (least severe) to 27 (most severe) were used to classify depression symptom severity. A PHQ-9 score of 10 or higher has been established as a cut-off point associated with symptoms of major depression in the general population (sensitivity, 74%; sensitivity 91%).[83] PHQ-9 scores were acquired from participant surveys administered during the visit most recent to the blood draw.

Dependent Variables

The biomarkers included in this analysis were selected and measured to answer HIV-specific research questions developed prior to our depression-specific aims in this analysis.

Therefore, we were limited to measuring inflammation, coagulation, monocyte activation, and altered metabolism using pre-existing lab results for interleukin-6, d-dimer, soluble CD14, and the basic metabolic panel, respectively. Although we used pre-existing laboratory data, these biomarkers were biologically plausible and warranted investigation for understanding depression physiology in HIV- and HIV+ adults.

Participant plasma in sodium citrate and serum were collected during a clinical visit between 2005 and 2006. Biomarkers were analyzed at the University of Vermont's Laboratory for Clinical Biochemistry Research. Serum concentration (pg/mL) of the inflammatory biomarker interleukin-6 (IL-6) was quantified by chemiluminescent sandwich enzyme-linked immunosorbent assay (ELISA) using R&D Systems, Inc. D-dimer, a marker of coagulation, was measured in participant plasma using the Stago STA-R Analyzer. The biomarker for monocyte activation, soluble CD14 (sCD14), was measured in serum (ng/mL) with sandwich ELISA on the R&D Systems analyzer. Serum glucose and lipid concentrations were obtained from VA laboratory records. **Figure 4-1** illustrates the timeline of independent and dependent variables.

Covariates

Administrative records were used to collect data regarding age, sex, and race/ethnicity. Outpatient medical, laboratory, and pharmacy records provided data on blood pressure, diabetes mellitus, hepatitis C virus (HCV) infection, HMG CoA reductase inhibitor (statin) use within six months of enrollment, alcohol abuse, and cocaine use. The VA collected health factor data regarding body mass index (BMI; kg/m^2) that was recorded in VA medical records.[50] Smoking status was reported via self-report surveys

Statistical analysis

Both the percentage of observed agreement and kappa statistic (κ) were calculated to understand the degree of agreement between our two classifications for depression: a diagnosis of MDD and a score of greater than or equal to 10 on the PHQ-9.[84]

We compared the prevalence of MDD and symptoms of major depression in HIV+ and HIV- participants using chi-square analysis. In a table of baseline characteristics stratified by HIV status and depression, continuous and categorical variables were compared using ANOVA and chi-square analyses, respectively.

For each HIV / depression group, we provided means with standard deviations for normally distributed biomarkers (sCD14, LDL-c, and HDL-c); and medians with interquartile ranges for non-normally distributed biomarkers (IL-6, d-dimer, glucose, and triglyceride). Within HIV strata, we compared mean and median biomarker concentrations in those with and without depression using two-sample T tests and Wilcoxon two-sample tests, as appropriate. Across the four groups, we compared biomarker concentrations using ANOVA. We also provided the proportion of participants with biomarker concentrations in the highest 75^{th} percentile for each HIV / depression group. These values were compared within HIV strata and across the four groups using chi-square analyses.

In standard multiple regression models, we modeled the association between MDD and the continuous biomarker concentrations (sCD14, LDL-c, and HDL-c) or log transformed biomarker concentrations (IL-6, d-dimer, glucose, and triglycerides). The multiplicative interactions between MDD and HIV infection were tested for significance. Models were adjusted for (1) HIV, age, sex, and race/ethnicity; and (2) HIV, age, sex, race/ethnicity, and variables that were significantly different between the four HIV / MDD groups in Table 4-3.

Using logistic regression, we determined whether the odds of having biomarker concentrations in the highest quartile were associated with MDD, adjusting for the same covariates listed above. In a second analysis, we stratified the models between MDD and biomarkers by HIV status. All of these models were repeated using the PHQ-9 criteria for depression. Significant associations were defined as those with p values < 0.05.

4.4 RESULTS

The prevalence of baseline MDD in this cohort of 2,099 veterans was 32.3%, while the prevalence of having recent symptoms of major depression using a PHQ-9 score of greater than or equal to ten was 21.7% (**Table 4-1**). The observed agreement between these two classifications was 71.6% ($\kappa = 0.29$). Kappa statistics ranging between 0.21 and 0.40 are interpreted as having fair agreement.[84]

The prevalence of MDD was not significantly different between HIV- and HIV+ participants (34.3% and 31.2%, respectively; $p = 0.14$; **Table 4-2**). A significantly higher proportion of HIV- participants had symptoms of major depression, i.e., PHQ-9 ≥ 10, (25.6%) compared to HIV+ participants (19.6%). Uninfected participants tended to have a higher frequency of PHQ-9 scores between 15 and 19, indicating symptoms of moderate major depression, and scores greater than or equal to 20 indicating symptoms of severe major depression.

Race / ethnicity, baseline diastolic blood pressure, and statin use within six months of enrollment were not significantly different across the four HIV / MDD groups (**Table 4-3**). The mean age was highest in the HIV- participants without MDD. Those with MDD were more

likely to be female, current smokers, have HCV infection, and use antidepressants. The HIV+ participants had lower BMIs and systolic blood pressures, were less likely to have diabetes and more likely to have HCV infection. In HIV+ participants, ART use was similar by depression status, but those with MDD tended to have higher HIV-1 RNA copies/mL and lower CD4:CD8 ratios. Baseline characteristics by HIV status and PHQ-9 score are provided in a Supplemental Table (**Table 4-10**).

In **Tables 4-4** and **4-5**, we provided mean concentrations for normally distributed biomarkers (sCD14, LDL-c, and HDL-c) and median concentrations for non-normally distributed biomarkers (IL-6, d-dimer, glucose, and triglyceride) by HIV / depression group. Among HIV- participants, those with MDD had higher concentrations of IL-6 and sCD14 compared to those without MDD (**Table 4-4**). Participants with HIV infection and co-occurring MDD had higher concentrations of glucose and triglycerides and lower concentrations of HDL-c compared to HIV+ participants without MDD. Using the PHQ-9 criteria, symptoms of major depression were associated with higher concentrations of IL-6 in the HIV- participants and with higher concentrations of triglycerides in the HIV+ participants (**Table 4-5**).

In standard multiple regression models, which included MDD, HIV infection, age, sex, and race/ethnicity, MDD was associated with higher concentrations of d-dimer and glucose (**Table 4-6**). Logistic regression models produced similar results: MDD was associated with concentrations of d-dimer and glucose in the highest quartile. In these models, HIV infection was associated with higher concentrations of IL-6 and triglycerides and lower concentrations of d-dimer, glucose, LDL-c, and HDL-c. In the fully adjusted models, MDD was associated with higher concentrations of LDL-c and glucose concentrations in the highest quartile. HIV infection was associated with higher concentrations of IL-6 (also, IL-6 concentrations in the

highest quartile), lower concentrations of d-dimer, and lower concentrations of HDL-c (also, having HDL-c concentrations that were not in the highest quartile).

Using the PHQ-9 definition for symptoms of major depression, scores greater than or equal to ten were associated with higher concentrations of IL-6 and triglycerides in the standard multiple regression models adjusting for HIV, age, sex, and race/ethnicity (**Table 4-7**) Only triglycerides were significantly higher in the fully adjusted models. Logistic regression models were not significant for this measure of depression. HIV infection remained significantly associated with higher concentrations of IL-6 and triglycerides and lower concentrations of d-dimer, glucose, LDL-c, and HDL-c in these models. In the fully adjusted models, HIV was associated with higher IL-6 and triglyceride concentrations and lower d-dimer and HDL-c concentrations.

There were significant multiplicative interactions between HIV and MDD in their associations with sCD14 ($p = 0.03$), HDL-c ($p = 0.01$), and triglycerides ($p = 0.02$). There were no significant multiplicative interactions between HIV and a PHQ-9 score ≥ 10. In response to these interactions, we explored the associations between depression and biomarkers in models stratified by HIV status.

In the HIV- participants, MDD was associated with higher concentrations of IL-6 and sCD14, adjusting for age, sex, and race/ethnicity (**Table 4-8**), while PHQ-9 scores ≥ 10 were associated with higher concentrations of IL-6 (**Table 4-9**). These associations were no longer significant in the fully adjusted models (i.e., age, sex, race/ethnicity, SBP, DBP, BMI, smoking, HCV infection, and antidepressant use).

In the HIV+ participants, MDD was associated with higher concentrations of glucose and lower concentrations of HDL-c, adjusting for age, sex, and race/ethnicity (**Table 4-8**), while

PHQ-9 scores ≥ 10 were associated with higher concentrations of triglycerides (**Table 4-9**). In the fully adjusted models, these associations were no longer significant, but MDD was associated with higher concentrations of sCD14 and interestingly, lower concentrations of IL-6.

4.5 DISCUSSION

In this study, we report that depression was associated with markers of inflammation and coagulation in the HIV- participants, but associated with markers of altered metabolism in the HIV+ participants, even after adjusting for BMI. Our findings were consistent using two definitions of depression (a baseline medical record diagnosis of MDD and self-reported symptoms of depression using the PHQ-9).

The finding that depression was significantly associated with IL-6 concentrations in HIV- participants is consistent with previous studies. Two meta-analyses, which included results from over 60 studies, reported that depression or depressive symptoms were positively associated with higher concentrations of IL-6.[1, 76] We found different results in the HIV+ participants. Median concentrations of IL-6 were not significantly different with MDD or with PHQ-9 scores ≥ 10. This result is consistent with one previous study that found no significant association between depressive symptoms and IL-6 in HIV+ participants.[85]

We found a significant association between MDD and higher concentrations of d-dimer in models adjusted for HIV, age, sex, and race/ethnicity, but the significance was lost in fully adjusted models. This finding supports previous studies that reported hypercoagulation with depression.[77] In the adjusted models stratified by HIV status, depression was not associated with d-dimer. HIV infection was associated with significantly lower concentrations of d-dimer.

Previous reports suggest that HIV is associated with higher concentrations of d-dimer when the viral infection is uncontrolled (HIV-RNA ≥ 500 copies/mL or CD4 count < 200 cells/μL).[80]

Previous findings between depression and monocyte activation are limited and mixed. One study found no association between MDD and levels of sCD14 and one study found that monocytes reacted less in response to an endotoxin challenge in vitro.[78, 86] In our study, the interaction between MDD and HIV was significant. MDD was associated with increased concentrations of sCD14 in the HIV- participants in the stratified model. There was no association in the HIV+ participants.

In fully adjusted models of the total sample, MDD was associated with higher concentrations of glucose and HDL-c, while a PHQ-9 score ≥ 10 was associated with higher concentrations of triglycerides. In stratified models, however, MDD and PHQ-9 scores ≥ 10 were not associated with any metabolic marker in the HIV- group. In the HIV+ participants, MDD was associated with an increased concentration of glucose and a decreased concentration of HDL-c, while PHQ-9 score ≥ 10 was associated with an increased concentration of triglycerides. HIV infection was associated with lower concentrations of glucose, LDL-c, and HDL-c, and higher concentrations of triglycerides in models adjusted for depression, age, sex, and race/ethnicity.

There are several limitations with this study. First, most of the participants were males and the findings may not generalize to females. Second, as our study is cross-sectional, we cannot determine directionality between depression and biomarker concentrations or causality. Third, our two definitions for depression had only fair agreement, which suggests that misclassification likely occurred. The baseline MDD diagnosis may be a marker of a more chronic exposure to the unhealthy effects of depression, while the PHQ-9 score ≥10 describes

recent symptoms. One explanation for this misclassification may be a result of effective MDD management. Since majority of the participants with MDD were prescribed antidepressants during the baseline period, depressive symptoms may have been effectively managed over time, resulting in PHQ-9 scores less than 10 during their visit between 2005 and 2006. Alternatively, participants may have developed MDD during the time period between April 1, 2003 and their visit between 2005 and 2006. These participants would be falsely classified as MDD negative. Despite differences in these definitions, depression influenced biomarker concentrations in similar ways. Last, biomarker concentrations were measured at a time point between 2005 and 2006, while baseline characteristics and the MDD diagnosis were determined during the baseline period (1998 – 2003). Biomarker concentrations may be influenced by more recent characteristics.

We hypothesized that co-occurring depression and HIV infection, which have overlapping physiological mechanisms, would interact and result in exaggerated increases in biomarkers of inflammation, coagulation, monocyte activation, and altered metabolism. Instead, our study provides new and interesting evidence that depression pathophysiology differs by HIV status. These findings are important to both investigators and clinicians. Studies that investigate the mechanism driving the association between depression and cardiovascular disease must consider co-occurring conditions, like HIV infection, in their analysis. To address symptoms of depression and their implications with cardiovascular disease, clinicians may need to consider interventions that address inflammation in HIV- patients and metabolism in HIV+ patients.

4.6 TABLES AND FIGURES

Table 4-1 Comparison between major depressive disorder and PHQ-9 Score ≥ 10

	MDD	No MDD	***Total Sample***
PHQ-9 score ≥ 10, n (%)	269 (12.8)	187 (8.9)	***456 (21.7)***
PHQ-9 score < 10, n (%)	409 (19.5)	1,234 (58.8)	***1,643 (78.3)***
Total sample	***678 (32.3)***	***1,421 (67.7)***	***2,099***

Abbreviations: MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire – 9 item

Table 4-2 Prevalence of major depressive disorder and depressive symptom severity among the total sample and by HIV infection status

		Total Sample (N = 2,099)	HIV- (N = 734)	HIV+ (N = 1,365)	P value
MDD, n (%)		678 (32.3)	252 (34.3)	426 (31.2)	0.14
PHQ-9 Scores					
< 10, n (%)	No major depression	1,643 (78.3)	546 (74.4)	1,097 (80.4)	**0.002**
10 – 14, n (%)	Mild major depression	214 (10.2)	78 (10.6)	136 (10.0)	0.63
15 – 19, n (%)	Moderate major depression	138 (6.6)	63 (8.6)	75 (5.5)	**0.007**
≥ 20, n (%)	Severe major depression	104 (5.0)	47 (6.4)	57 (4.2)	**0.02**

Abbreviations: HIV, human immunodeficiency virus; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire – 9 item

Table 4-3 Baseline participant characteristics by HIV status and major depressive disorder diagnosis (N = 2,099)

	HIV-uninfected		**HIV-infected**		
Characteristic	**No MDD (*n* = 482)**	**MDD (*n* = 252)**	**No MDD (*n* = 939)**	**MDD (*n* = 426)**	***P***
Age, years, mean (SD)	54.7 (10.0)	51.9 (7.2)	51.9 (8.2)	51.8 (7.7)	**<.0001**
Male, %	90.0	88.9	97.2	96.5	**<.0001**
African American, %	67.0	65.5	71.0	64.6	
White, %	21.6	20.6	17.8	20.2	0.2107
Hispanic, %	7.5	8.3	8.1	10.1	
Other, %	3.9	5.6	3.1	5.2	
BMI, kg/m^2, mean (SD)	30.3 (6.3)	29.6 (6.5)	25.7 (4.8)	26.2 (4.9)	**<.0001**
Systolic blood pressure, mean (SD)	132.0 (14.3)	130.8 (14.8)	128.0 (14.2)	129.3 (15.0)	**<.0001**
Diastolic blood pressure, mean (SD)	78.4 (9.4)	78.9 (10.4)	78.0 (9.0)	79.1 (9.6)	0.1801
Diabetes mellitus, %	38.6	40.5	24.8	31.7	**<.0001**
Statin use, %	15.4	15.5	12.8	17.4	0.1396
Current smoking, %	40.2	64.0	48.5	55.2	
Past, %	29.5	17.0	23.9	25.7	**<.0001**
Never, %	30.3	19.0	27.6	19.1	
Alcohol abuse, %	35.9	66.3	29.9	55.9	**<.0001**
Cocaine use, %	27.2	59.5	26.3	52.6	**<.0001**
HCV infection, %	27.4	43.3	45.2	57.0	**<.0001**

Table 4-3 Continued

	HIV-uninfected		HIV-infected		
Characteristic	**No MDD (*n* = 482)**	**MDD (*n* = 252)**	**No MDD (*n* = 939)**	**MDD (*n* = 426)**	***P***
Any antidepressant use, %	13.1	54.8	15.6	54.7	**<.0001**
SSRI use, %	7.7	42.9	7.6	39.9	**<.0001**
TCA use, %	2.1	6.0	4.8	10.3	**<.0001**
Other antidepressant use, %	7.7	40.9	7.8	39.2	**<.0001**
ART use, %	--	--	93.6	94.8	0.3773
HIV-1 RNA, copies/mL, median (IQR)	--	--	75.0 (50.0, 2340.0)	75.0 (75.0, 6031.0)	**0.0205**
CD4, median (IQR)	--	--	408.5 (269.0, 602.0)	399.0 (232.0, 585.0)	0.3131
CD4 nadir, median (IQR)	--	--	190.0 (72.0, 302.0)	182.0 (77.0, 282.0)	0.4305
CD8, mean (SD)	--	--	965.0 (518.1)	979.8 (508.6)	0.6680
CD4:CD8, median (IQR)	--	--	0.50 (0.30, 0.70)	0.40 (0.20, 0.70)	**0.0388**

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants

Table 4-4 Biomarker profiles by HIV status and major depressive disorder (MDD) diagnosis (N = 2,099)

			HIV-uninfected		P for	HIV-infected		P for	P across
	Biomarker		**No MDD (*n* = 482)**	**MDD (*n* = 252)**	**HIV-**	**No MDD (*n* = 939)**	**MDD (*n* = 426)**	**HIV+**	**groups**
Inflammation		N = 2064	470	245		925	424		
	IL-6	Median (IQR)	1.67 (1.11, 2.87)	1.92 (1.22, 3.29)	**0.0444**	1.92 (1.37, 3.24)	2.10 (1.41, 3.40)	0.2765	**<0.0001**
		> 75th percentile	21.3%	27.4%	0.0686	25.5%	26.7%	0.6579	0.1761
Coagulation		N = 2070	474	246		926	424		
	D-dimer	Median (IQR)	0.29 (0.21, 0.50)	0.31 (0.21, 0.53)	0.4763	0.26 (0.15, 0.45)	0.29 (0.16, 0.54)	0.0699	**<0.0001**
		> 75th percentile	24.9%	26.8%	0.5724	22.1%	26.2%	0.1036	0.2502
Monocyte Activation		N = 2074	476	246		928	424		
	sCD14	Mean (SD)	1766.3 (471.1)	1862.7 (489.8)	**0.0104**	1804.6 (555.8)	1791.9 (511.1)	0.6812	0.1261
		> 75th percentile	21.0%	30.5%	**0.0048**	26.0%	24.3%	0.5112	**0.0356**
Metabolic Markers		N = 2093	479	250		938	426		
	Glucose	Median (IQR)	100.0 (89.0, 115.0)	100.0 (88.0, 117.0)	0.6042	96.0 (87.0, 107.0)	97.5 (88.0, 115.0)	**0.0125**	**<0.0001**
		> 75th percentile	28.8%	31.6%	0.4342	18.3%	27.2%	**0.0002**	**<0.0001**
		N = 2035	464	240		918	413		
	LDL-c	Mean (SD)	103.9 (33.0)	106.8 (39.1)	0.6010	100.4 (34.6)	99.1 (33.9)	0.5350	0.0572
		> 75th percentile	25.7%	30.0%	0.2182	24.5%	21.6%	0.2393	0.1099
		N = 2043	468	241		921	413		
	HDL-c	Mean (SD)	46.8 (14.2)	48.0 (17.6)	0.7326	45.3 (17.1)	42.5 (14.9)	**0.0073**	**<0.0001**
		> 75th percentile	26.1%	26.6%	0.8888	24.7%	19.4%	**0.0343**	0.0725
		N = 2065	469	245		930	421		
	Triglycerides	Median (IQR)	120.0 (79.0, 174.0)	104.0 (77.0, 158.0)	0.0866	135.5 (88.0, 205.0)	147.0 (94.0, 221.0)	**0.0243**	**<0.0001**
		> 75th percentile	17.9%	17.6%	0.9051	27.3%	30.2%	0.2802	**<0.0001**

Abbreviations: HDL-c, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IL-6, interleukin-6; LDL-c, low-density lipoprotein cholesterol; MDD, major depressive disorder; sCD14, soluble CD14

Table 4-5 Biomarker profiles by HIV status and symptoms of major depression (PHQ-9 ≥ 10) (N = 2,099)

			HIV-uninfected		P for	HIV-infected		P for	P across
	Biomarker		**PHQ-9 < 10 (*n* = 546)**	**PHQ-9 ≥ 10 (*n* = 188)**	**HIV-**	**PHQ-9 < 10 (*n* = 1097)**	**PHQ-9 ≥ 10 (*n* = 268)**	**HIV+**	**groups**
Inflammation	IL-6	N = 2064	534	181		1083	266		
		Median (IQR)	1.69 (1.13, 2.78)	1.97 (1.27, 3.38)	**0.0261**	1.98 (1.38, 3.28)	2.11 (1.41, 3.24)	0.5088	**<0.0001**
		> 75th percentile	21.4%	29.3%	**0.0292**	26.0%	25.2%	0.7765	0.1025
Coagulation	D-dimer	N = 2070	538	182		1085	265		
		Median (IQR)	0.30 (0.21, 0.53)	0.31 (0.21, 0.47)	0.9900	0.26 (0.15, 0.47)	0.28 (0.18, 0.50)	0.2437	**<0.0001**
		> 75th percentile	26.2%	23.6%	0.4900	23.1%	24.5%	0.6307	0.5926
Monocyte Activation	sCD14	N = 2074	540	182		1086	266		
		Mean (SD)	1788.2 (473.0)	1831.6 (497.9)	0.2909	1705.5 (1430.9)	1794.0 (535.9)	0.8249	0.8009
		> 75th percentile	23.0%	28.0%	0.1684	26.0%	23.3%	0.3723	0.3876
Metabolic Markers	Glucose	N = 2093	541	188		1096	268		
		Median (IQR)	100.0 (89.0, 116.0)	102.0 (90.5, 117.5)	0.2274	96.0 (88.0, 109.0)	96.0 (87.0, 110.0)	0.7499	**0.0007**
		> 75th percentile	29.0%	31.9%	0.4546	21.0%	21.6%	0.8134	**0.0002**
	LDL-c	N = 2035	523	181		1072	259		
		Mean (SD)	106.1 (34.1)	101.4 (38.1)	0.0640	100.4 (33.9)	98.4 (36.3)	0.3910	**0.0063**
		> 75th percentile	27.3%	26.5%	0.8301	23.9%	22.4%	0.6130	0.3356
	HDL-c	N = 2043	526	183		1074	260		
		Mean (SD)	47.3 (15.8)	47.1 (14.4)	0.6041	44.9 (16.9)	42.7 (14.6)	0.1878	**<0.0001**
		> 75th percentile	25.1%	29.5%	0.2424	23.6%	20.8%	0.3380	0.1751
	Triglycerides	N = 2065	530	184		1087	264		
		Median (IQR)	113.5 (75.0, 165.0)	118.0 (83.5, 178.5)	0.1157	135.0 (88.0, 203.0)	156.5 (100.0, 238.0)	**0.0006**	**<0.0001**
		> 75th percentile	16.8%	20.7%	0.2382	26.9%	33.7%	**0.0265**	**<0.0001**

Abbreviations: HDL-c, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IL-6, interleukin-6; LDL-c, low-density lipoprotein cholesterol; PHQ-9, nine item Patient Health Questionnaire; sCD14, soluble CD14

Table 4-6 Association between major depressive disorder, HIV infection, and biomarker concentrations, in two models adjusting for covariates

Table 4-6a	**IL-6** (N = 2064)		**D-dimer** (N = 2070)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 1	(continuous; log)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
MDD vs. no MDD	0.06 (-0.01, 0.13)	1.22 (0.98, 1.51)	**0.09 (0.01, 0.18)***	**1.26 (1.01, 1.56)***
HIV+ vs. HIV-	**0.14 (0.06, 0.21)***	1.24 (1.00, 1.54)	**-0.18 (-0.27, -0.10)***	0.94 (0.76, 1.17)
Age (years)	**0.01 (0.01, 0.02)***	**1.03 (1.02, 1.04)***	**0.02 (0.01, 0.02)***	**1.04 (1.02, 1.05)***
Sex	-0.02 (-0.17, 0.14)	0.97 (0.61, 1.56)	-0.06 (-0.24, 0.12)	1.29 (0.78, 2.13)
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	0.04 (-0.05, 0.13)	1.08 (0.83, 1.40)	**0.15 (0.05, 0.26)***	**1.67 (1.26, 2.21)***
Hispanic	0.10 (-0.04, 0.24)	1.37 (0.92, 2.05)	0.05 (-0.11, 0.22)	1.31 (0.84, 2.04)
Other	0.16 (-0.02, 0.35)	1.02 (0.59, 1.79)	0.13 (-0.09, 0.35)	1.36 (0.76, 2.42)

Table 4-6b	**IL-6** (N = 2042)		**D-dimer** (N = 2048)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 2	(continuous; log)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
MDD vs. no MDD	-0.06 (-0.13, 0.02)	0.93 (0.73, 1.18)	-0.01 (-0.10, 0.09)	1.02 (0.80, 1.31)
HIV+ vs. HIV-	**0.19 (0.12, 0.27)***	**1.32 (1.04, 1.68)***	**-0.15 (-0.25, -0.06)***	1.02 (0.80, 1.29)
Age (years)	**0.02 (0.01, 0.02)***	**1.04 (1.02, 1.05)***	**0.02 (0.01, 0.02)***	**1.04 (1.02, 1.05)***
Sex	-0.07 (-0.22, 0.08)	0.82 (0.51 1.32)	-0.09 (-0.27, 0.10)	1.23 (0.74, 2.03)
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	-0.02 (-0.10, 0.07)	0.93 (0.71, 1.22)	**0.12 (0.01, 0.22)***	**1.56 (1.17, 2.09)***
Hispanic	0.06 (-0.08, 0.20)	1.30 (0.86, 1.95)	0.03 (-0.14, 0.20)	1.28 (0.82, 2.00)
Other	0.06 (-0.12, 0.24)	0.90 (0.51, 1.59)	0.10 (-0.13, 0.32)	1.25 (0.70, 2.25)
BMI	**0.02 (0.01, 0.02)***	**1.03 (1.00, 1.05)***	0.005 (-0.002, 0.01)	1.01 (0.99, 1.03)
Systolic blood pressure	-0.002 (-0.005, 0.001)	1.00 (0.99, 1.01)	0.002 (-0.002, 0.006)	1.01 (1.00, 1.02)
Diastolic blood pressure	0.003 (-0.002, 0.008)	1.01 (1.00, 1.03)	-0.001 (-0.007, 0.005)	1.00 (0.98, 1.01)
Diabetes				
Never smoking	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Current	**0.18 (0.10, 0.27)***	**1.69 (1.28, 2.23)***	**0.13 (0.02, 0.23)***	**1.25 (0.95, 1.64)***
Past	-0.04 (-0.14, 0.06)	0.94 (0.69, 1.29)	-0.05 (-0.17, 0.06)	0.96 (0.71, 1.31)
HCV infection	**0.12 (0.05, 0.19)***	**1.31 (1.05, 1.64)***	0.01 (-0.08, 0.10)	0.97 (0.77, 1.21)
Antidepressant Use	**0.19 (0.10, 0.27)***	**1.47 (1.15, 1.89)***	**0.18 (0.08, 0.28)***	**1.53 (1.19, 1.96)***

Table 4-6 Continued

Table 4-6c	**sCD14** (N = 2074)		**Glucose** (N = 2093)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 1	(continuous)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
MDD vs. no MDD	29.7 (-18.2, 77.5)	1.15 (0.93, 1.42)	**0.04 (0.01, 0.06)***	**1.49 (1.20, 1.84)***
HIV+ vs. HIV-	17.4 (-30.4, 65.2)	1.10 (0.89, 1.36)	**-0.03 (-0.05, -0.002)***	**0.67 (0.54, 0.83)***
Age (years)	**6.03 (3.35, 8.71)***	**1.02 (1.01, 1.03)***	**0.005 (0.003, 0.006)***	**1.04 (1.03, 1.05)***
Sex	-24.1 (-123.8, 75.7)	0.92 (0.59, 1.45)	0.01 (-0.04, 0.06)	1.10 (0.68, 1.76)
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	**-85.0 (-142.8, -27.3)***	0.81 (0.63, 1.04)	0.003 (-0.03, 0.03)	1.03 (0.79, 1.35)
Hispanic	-2.6 (-94.8, 89.5)	0.99 (0.66, 1.47)	0.03 (-0.02, 0.08)	**1.72 (1.15, 2.56)***
Other	-63.0 (-184.8, 58.9)	0.80 (0.46, 1.39)	0.05 (-0.02, 0.12)	1.24 (0.72, 2.14)

Table 4-6d	**sCD14** (N = 2052)		**Glucose** (N = 2074)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 2	(continuous)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
MDD vs. no MDD	-35.1 (-87.2, 17.1)	0.91 (0.72, 1.16)	0.02 (-0.006, 0.05)	**1.39 (1.09, 1.77)***
HIV+ vs. HIV-	-42.9 (-93.8, 7.97)	0.88 (0.70, 1.12)	0.007 (-0.02, 0.03)	0.87 (0.69, 1.11)
Age (years)	**6.45 (3.65, 9.26)***	**1.02 (1.01, 1.03)***	**0.004 (0.003, 0.006)***	**1.04 (1.02, 1.05)***
Sex	-55.3 (-154.1, 43.4)	0.82 (0.51, 1.29)	0.007 (-0.05, 0.06)	1.08 (0.67, 1.77)
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	**-119.4 (-177.4, -61.3)***	0.72 (0.55, 0.93)	-0.005 (-0.04, 0.03)	0.98 (0.74, 1.29)
Hispanic	-16.4 (-107.5, 74.7)	0.94 (0.62, 1.40)	0.02 (-0.03, 0.07)	**1.65 (1.10, 2.48)***
Other	-65.0 (-186.0, 56.0)	0.77 (0.44, 1.35)	0.03 (-0.04, 0.09)	1.00 (0.57, 1.76)
Systolic blood pressure	-1.78 (-3.99, 0.43)	1.00 (0.99, 1.01)	**0.002 (0.0003, 0.003)***	**1.02 (1.01, 1.03)***
Diastolic blood pressure	3.55 (0.23, 6.87)	1.01 (0.99, 1.02)	-0.001 (-0.003, 0.001)	**0.98 (0.97, 1.00)***
BMI	**-8.77 (-13.1, -4.45)***	**0.96 (0.94, 0.98)***	**0.008 (0.006, 0.01)***	**1.07 (1.05, 1.09)***
Never smoking	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Current	**60.6 (3.29, 118.0)***	1.56 (0.88, 1.51)	-0.006 (-0.04, 0.02)	0.95 (0.72, 1.26)
Past	-22.0 (-85.9, 42.0)	0.93 (0.69, 1.27)	0.01 (-0.02, 0.05)	1.14 (0.85, 1.54)
HCV infection	**88.2 (39.6, 136.8)***	**1.41 (1.13, 1.76)***	**0.03 (0.001, 0.05)***	**1.32 (1.04, 1.66)***
Antidepressant Use	**114.1 (59.0, 169.2)***	**1.49 (1.17, 1.90)***	0.02 (-0.007, 0.05)	1.17 (0.91, 1.51)

Table 4-6 Continued

Table 4-6e	**LDL-c** (N = 2035)		**HDL-c** (N = 2043)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 1	(continuous)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
MDD vs. no MDD	0.20 (-3.03, 3.43)	0.96 (0.77, 1.20)	-1.12 (-2.60, 0.36)	0.87 (0.70, 1.09)
HIV+ vs. HIV-	**-5.51 (-8.73, -2.28)***	**0.80 (0.65, 0.99)***	**-2.21 (-3.68, -0.74)***	0.91 (0.73, 1.13)
Age (years)	**-0.27 (-0.45, -0.09)***	**0.98 (0.97, 0.99)***	**0.09 (0.008, 0.17)***	**1.00 (1.00, 1.03)***
Sex	1.26 (-5.48, 8.00)	1.06 (0.68, 1.66)	**-8.06 (-11.1, -5.00)***	**0.40 (0.27, 0.61)***
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	-2.80 (-6.68, 1.08)	0.90 (0.69, 1.16)	**6.49 (4.72, 8.26)***	**2.04 (1.52, 2.74)***
Hispanic	**-7.76 (-13.9, -1.60)***	0.73 (0.47, 1.12)	2.19 (-0.63, 5.01)	0.96 (0.59, 1.58)
Other	**-12.4 (-20.6, -4.18)***	0.66 (0.37, 1.20)	1.59 (-2.18, 5.35)	1.08 (0.57, 2.04)

Table 4-6f	**LDL-c** (N = 2019)		**HDL-c** (N = 2026)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 2	(continuous)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
MDD vs. no MDD	**3.94 (0.43, 7.45)***	1.21 (0.95, 1.55)	-0.33 (-1.94, 1.28)	0.92 (0.71, 1.19)
HIV+ vs. HIV-	-1.50 (-4.93, 1.94)	0.97 (0.76, 1.23)	**-4.51 (-6.08, -2.94)***	**0.64 (0.50, 0.82)***
Age (years)	-0.19 (-0.38, 0.0002)	**0.98 (0.97, 0.99)***	0.07 (-0.02, 0.15)	1.01 (1.00, 1.03)
Sex	3.34 (-3.30, 9.99)	1.21 (0.77, 1.90)	**-8.23 (-11.3, -5.20)***	**0.37 (0.24, 0.56)***
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	-0.12 (-4.00, 3.76)	1.04 (0.80, 1.36)	**6.43 (4.65, 8.20)***	**1.98 (1.46, 2.68)***
Hispanic	-5.47 (-11.5, 0.60)	0.81 (0.52, 1.25)	2.60 (-0.18, 5.39)	1.00 (0.60, 1.66)
Other	**-11.2 (-19.3, -3.01)***	0.72 (0.40, 1.33)	2.94 (-0.79, 6.68)	1.22 (0.63, 2.37)
Systolic blood pressure	-0.04 (-0.18, 0.11)	1.00 (0.99, 1.01)	0.06 (-0.01, 0.12)	**1.01 (1.00, 1.02)**
Diastolic blood pressure	0.17 (-0.05, 0.39)	1.00 (0.99, 1.02)	-0.004 (-0.11, 0.10)	1.00 (0.57, 1.02)
BMI	**0.40 (0.12, 0.69)***	**1.02 (1.00, 1.04)***	**-0.61 (-0.74, -0.48)***	**0.90 (0.88, 0.93)***
Never smoking	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Current	-0.67 (-4.52, 3.18)	0.92 (0.70, 1.19)	-0.96 (-2.73, 0.80)	**0.95 (0.72, 1.25)**
Past	-0.28 (-4.55, 4.00)	1.03 (0.78, 1.38)	-1.44 (-3.40, 0.52)	0.82 (0.60, 1.13)
HCV infection	**-13.3 (-16.6, -10.0)***	**0.49 (0.39, 0.62)***	-0.58 (-2.08, 0.91)	0.95 (0.75, 1.20)
Antidepressant Use	**-4.48 (-8.18, -0.77)***	**0.75 (0.57, 0.98)***	-1.52 (-3.22, 0.18)	0.87 (0.66, 1.14)

Table 4-6 Continued

Table 4-6g	**Triglyceride** (N = 2065)	
	β (95% CI)	**OR (95% CI)**
Model 1	(continuous)	(> 75th percentile)
MDD vs. no MDD	0.01 (-0.04, 0.07)	1.05 (0.84, 1.31)
HIV+ vs. HIV-	**0.18 (0.13, 0.24)***	**1.92 (1.52, 2.44)**
Age (years)	-0.00001 (-0.003, 0.003)	1.00 (0.99, 1.02)
Sex	**0.13 (0.007, 0.25)***	1.48 (0.86, 2.54)
White	[Reference]	1.00 [Reference]
Black	**-0.26 (-0.33, -0.19)***	**0.46 (0.36, 0.59)**
Hispanic	-0.03 (-0.14, 0.08)	0.96 (0.66, 1.41)
Other	-0.06 (-0.21, 0.09)	0.92 (0.55, 1.54)

Table 4-6h	**Triglyceride** (N = 2049)	
	β (95% CI)	**OR (95% CI)**
Model 2	(continuous)	(> 75th percentile)
MDD vs. no MDD	-0.02 (-0.08, 0.04)	0.96 (0.75, 1.22)
HIV+ vs. HIV-	**0.28 (0.22, 0.34)***	**2.45 (1.88, 3.18)***
Age (years)	0.001 (-0.003, 0.004)	1.00 (0.99, 1.02)
Sex	**0.12 (-0.001, 0.24)***	1.44 (0.83, 2.49)
White	[Reference]	1.00 [Reference]
Black	**-0.27 (-0.34, -0.20)***	**0.43 (0.33, 0.56)***
Hispanic	-0.04 (-0.15, 0.06)	0.92 (0.63, 1.35)
Other	-0.14 (-0.29, 0.005)	0.76 (0.45, 1.29)
Systolic blood pressure	-0.002 (-0.004, 0.001)*	1.00 (0.99, 1.01)
Diastolic blood pressure	**0.006 (0.002, 0.01)***	1.02 (1.00, 1.03)
BMI	**0.02 (0.02, 0.03)***	**1.05 (1.03, 1.08)***
Never smoking	[Reference]	1.00 [Reference]
Current	0.01 (-0.06, 0.08)	1.08 (0.82, 1.42)
Past	0.07 (-0.003, 0.15)	1.24 (0.92, 1.67)
HCV infection	0.04 (-0.02, 0.09)	1.12 (0.89, 1.41)
Antidepressant Use	0.05 (-0.02, 0.11)	1.14 (0.88, 1.48)

Table 4-7 Association between symptoms of major depression (PHQ-9 ≥ 10), HIV infection, and biomarker concentrations, in two models adjusting for covariates

Table 4-7a	**IL-6** (N = 2064)		**D-dimer** (N = 2070)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 1	(continuous; log)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
PHQ-9 ≥ 10 vs. < 10	**0.09 (0.01, 0.17)***	1.17 (0.92, 1.49)	0.06 (-0.04, 0.16)	1.12 (0.87, 1.44)
HIV+ vs. HIV-	**0.14 (0.07, 0.21)***	1.24 (1.00, 1.55)	**-0.18 (-0.27, -0.10)***	0.94 (0.76, 1.17)
Age (years)	**0.01 (0.01, 0.02)***	**1.03 (1.02, 1.04)***	**0.02 (0.01, 0.02)***	**1.04 (1.02, 1.05)***
Sex	-0.02 (-0.17, 0.14)	0.97 (0.61, 1.56)	-0.06 (-0.24, 0.12)	1.29 (0.78, 2.12)
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	0.04 (-0.05, 0.13)	1.08 (0.83, 1.41)	**0.15 (0.05, 0.26)***	**1.66 (1.25, 2.20)***
Hispanic	0.10 (-0.04, 0.24)	1.37 (0.92, 2.05)	0.05 (-0.12, 0.22)	1.31 (0.84, 2.04)
Other	0.17 (-0.02, 0.35)	1.04 (0.59, 1.81)	0.14 (-0.08, 0.36)	1.38 (0.78, 2.45)

Table 4-7b	**IL-6** (N = 2042)		**D-dimer** (N = 2048)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 2	(continuous; log)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
PHQ-9 ≥ 10 vs. < 10	0.005 (-0.08, 0.09)	0.95 (0.74, 1.22)	-0.001 (-0.10, 0.10)	0.98 (0.75, 1.27)
HIV+ vs. HIV-	**0.19 (0.12, 0.27)***	**1.32 (1.04, 1.68)***	**-0.15 (-0.25, -0.06)***	1.01 (0.80, 1.28)
Age (years)	**0.02 (0.01, 0.02)***	**1.04 (1.02, 1.05)***	**0.02 (0.01, 0.02)***	**1.04 (1.02, 1.05)***
Sex	-0.07 (-0.22, 0.08)	0.82 (0.51, 1.32)	-0.09 (-0.27, 0.10)	1.22 (0.74, 2.03)
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	-0.01 (-0.10, 0.08)	0.93 (0.71, 1.22)	**0.12 (0.01, 0.22)***	**1.56 (1.17, 2.08)***
Hispanic	0.06 (-0.08, 0.20)	1.30 (0.86, 1.95)	0.03 (-0.14, 0.20)	1.28 (0.82, 2.00)
Other	0.06 (-0.12, 0.24)	0.90 (0.51, 1.59)	0.10 (-0.13, 0.32)	1.25 (0.70, 2.25)
Systolic blood pressure	-0.002 (-0.005, 0.001)	1.00 (0.99, 1.01)	0.002 (-0.002, 0.006)	1.01 (1.00, 1.02)
Diastolic blood pressure	0.003 (-0.002, 0.008)	1.01 (1.00 1.03)	-0.001 (-0.007, 0.005)	1.00 (0.98, 1.01)
BMI	**0.02 (0.01, 0.02)***	**1.03 (1.00, 1.05)***	0.005 (-0.003, 0.01)	1.01 (0.99, 1.03)
Never smoking	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Current	**0.18 (0.09, 0.26)***	**1.69 (1.28, 2.23)***	**0.13 (0.02, 0.23)***	1.25 (0.95, 1.65)
Past	-0.04 (-0.14, 0.05)	0.94 (0.68, 1.29)	-0.05 (-0.17, 0.06)	0.96 (0.71, 1.31)
HCV infection	**0.12 (0.04, 0.19)***	**1.31 (1.05, 1.64)***	0.01 (-0.08, 0.10)	0.97 (0.77, 1.22)
Antidepressant Use	**0.16 (0.08, 0.24)***	**1.44 (1.15, 1.81)***	**0.18 (0.09, 0.28)***	**1.55 (1.23, 1.96)***

Table 4-7 Continued

Table 4-7c	**sCD14** (N = 2074)		**Glucose** (N = 2093)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 1	(continuous)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
PHQ-9 ≥ 10 vs. < 10	14.2 (-40.5, 69.0)	1.03 (0.81, 1.32)	0.002 (-0.03, 0.03)	1.13 (0.88, 1.45)
HIV+ vs. HIV-	17.4 (-30.5, 65.2)	1.10 (0.88, 1.36)	**-0.03 (-0.06, -0.003)***	**0.67 (0.54, 0.83)***
Age (years)	**6.00 (3.11, 8.68)***	**1.02 (1.01, 1.03)***	**0.005 (0.003, 0.006)***	**1.04 (1.03, 1.05)***
Sex	-24.4 (-124.2, 75.5)	0.92 (0.59, 1.44)	0.01 (-0.04, 0.06)	1.09 (0.68, 1.75)
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	**-85.1 (-143.0, -27.2)***	0.81 (0.63, 1.04)	0.001 (-0.03, 0.03)	1.02 (0.79, 1.34)
Hispanic	-2.60 (-94.8, 89.6)	0.99 (0.66, 1.47)	0.03 (-0.02, 0.08)	**1.72 (1.16, 2.56)***
Other	-60.8 (-182.7, 61.0)	0.81 (0.47, 1.04)	0.05 (-0.01, 0.12)	1.27 (0.74, 2.19)

Table 4-7d	**sCD14** (N = 2052)		**Glucose** (N = 2074)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 2	(continuous)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
PHQ-9 ≥ 10 vs. < 10	-25.9 (-81.4, 29.7)	0.91 (0.71, 1.18)	-0.01 (-0.04, 0.02)	1.01 (0.78, 1.31)
HIV+ vs. HIV-	-43.2 (-94.1, 7.75)	0.88 (0.70, 1.11)	0.005 (-0.02, 0.03)	0.87 (0.69, 1.10)
Age (years)	**6.47 (3.66, 9.28)***	**1.02 (1.01, 1.03)***	**0.004 (0.003, 0.006)***	**1.04 (1.02, 1.05)***
Sex	-54.7 (-153.5, 44.1)	0.82 (0.51, 1.29)	0.005 (-0.05, 0.06)	1.07 (0.65, 1.74)
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	**-119.4 (-177.6, -61.2)***	**0.72 (0.55, 0.93)***	-0.008 (-0.04, 0.02)	0.95 (0.72, 1.26)
Hispanic	-15.7 (-106.8, 75.4)	0.94 (0.62, 1.41)	0.02 (-0.03, 0.07)	**1.64 (1.09, 2.46)***
Other	-65.5 (-186.5, 55.6)	0.77 (0.44, 1.35)	0.03 (-0.04, 0.09)	1.00 (0.57, 1.76)
Systolic blood pressure	-1.81 (-4.02, 0.40)	1.00 (0.98, 1.01)	**0.001 (0.0003, 0.003)***	**1.02 (1.01, 1.03)***
Diastolic blood pressure	**3.55 (0.23, 6.87)***	1.01 (0.99, 1.02)	-0.0006 (-0.002, 0.001)	**0.99 (0.97, 1.00)***
BMI	**-8.73 (-13.1, -4.39)***	**0.96 (0.94, 0.98)***	**0.009 (0.006, 0.01)***	**1.07 (1.05, 1.09)***
Never smoking	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Current	**59.6 (2.20, 116.9)***	1.15 (0.88, 1.51)	-0.003 (-0.03, 0.03)	0.97 (0.74, 1.29)
Past	-23.7 (-87.7, 40.2)	0.93 (0.68, 1.26)	0.01 (-0.02, 0.05)	1.15 (0.86, 1.55)
HCV infection	**88.1 (39.5, 136.8)***	**1.41 (1.13, 1.76)***	**0.03 (0.003, 0.06)***	**1.33 (1.06, 1.68)***
Antidepressant Use	**103.8 (52.3, 155.2)***	**1.46 (1.16, 1.83)***	**0.03 (0.006, 0.06)***	**1.34 (1.06, 1.70)***

Table 4-7 Continued

Table 4-7e	**LDL-c** (N = 2035)		**HDL-c** (N = 2043)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 1	(continuous)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
PHQ-9 ≥ 10 vs. < 10	-3.29 (-6.98, 0.39)	0.90 (0.70, 1.16)	-0.83 (-2.52, 0.85)	1.08 (0.84, 1.39)
HIV+ vs. HIV-	**-5.73 (-8.97, -2.50)***	**0.80 (0.64, 0.99)***	**-2.23 (-3.70, -0.75)***	0.92 (0.73, 1.14)
Age (years)	**-0.28 (-0.46, -0.10)***	**0.98 (0.97, 0.99)***	**0.09 (0.008, 0.17)***	**1.02 (1.00, 1.03)***
Sex	1.13 (-5.61, 7.86)	1.06 (0.68, 1.65)	**-8.06 (-11.1, -5.00)***	**0.41 (0.27, 0.61)***
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	-3.03 (-6.91, 0.86)	0.89 (0.69, 1.16)	**6.48 (4.70, 8.25)***	**2.06 (1.54, 2.77)***
Hispanic	**-7.61 (-13.8, -1.45)***	0.73 (0.48, 1.24)	2.21 (-0.61, 5.03)	0.95 (0.58, 1.57)
Other	**-12.3 (-20.5, -4.07)***	0.66 (0.37, 1.20)	1.51 (-2.26, 5.27)	1.06 (0.56, 2.01)

Table 4-7f	**LDL-c** (N = 2019)		**HDL-c** (N = 2026)	
	β (95% CI)	**OR (95% CI)**	**β (95% CI)**	**OR (95% CI)**
Model 2	(continuous)	(> 75th percentile)	(continuous; log)	(> 75th percentile)
PHQ-9 ≥ 10 vs. < 10	-1.45 (-5.18, 2.28)	1.03 (0.79, 1.34)	0.03 (-1.67, 1.74)	1.21 (0.92, 1.58)
HIV+ vs. HIV-	-1.66 (-5.10, 1.78)	0.97 (0.76, 1.23)	**-4.50 (-6.07, -2.93)***	**0.65 (0.51, 0.83)***
Age (years)	**-0.20 (-0.39, -0.01)***	**0.98 (0.97, 0.99)***	0.07 (-0.02, 0.15)	1.01 (1.00, 1.03)
Sex	3.05 (-3.61, 9.70)	1.20 (0.76, 1.89)	**-8.21 (-11.2, -5.18)***	**0.37 (0.24, 0.57)***
White	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Black	-0.54 (-4.43, 3.35)	1.03 (0.79, 1.35)	**6.45 (4.67, 8.24)***	**2.02 (1.49, 2.74)***
Hispanic	-5.49 (-11.6, 0.59)	0.80 (0.52, 1.24)	2.61 (-0.18, 5.39)	1.00 (0.60, 1.66)
Other	**-11.1 (-19.3, -2.99)***	0.72 (0.40, 1.33)	2.94 (-0.80, 6.68)	1.22 (0.63, 2.37)
Systolic blood pressure	-0.04 (-0.19, 0.11)	1.00 (0.99, 1.01)	0.06 (-0.01, 0.12)	1.01 (1.00, 1.02)
Diastolic blood pressure	0.18 (-0.04, 0.41)	1.00 (0.99, 1.02)	-0.005 (-0.11, 0.10)	1.00 (0.99, 1.02)
BMI	**0.43 (0.14, 0.72)***	**1.02 (1.00, 1.04)***	**-0.61 (-0.74, -0.48)***	**0.90 (0.88, 0.92)***
Never smoking	[Reference]	1.00 [Reference]	[Reference]	1.00 [Reference]
Current	-0.23 (-4.08, 3.63)	0.93 (0.72, 1.21)	-0.99 (-2.76, 0.77)	0.93 (0.70, 1.22)
Past	-0.09 (-4.37, 4.18)	1.05 (0.78, 1.40)	-1.46 (-3.42, 0.50)	0.82 (0.60, 1.13)
HCV infection	**-13.1 (-16.3, -9.80)***	**0.49 (0.39, 0.62)***	-0.60 (-2.10, 0.90)	0.93 (0.74, 1.18)
Antidepressant Use	-2.61 (-6.07, 0.85)	0.81 (0.63, 1.04)	**-1.66 (-3.25, -0.08)***	0.82 (0.63, 1.05)

Table 4-7 Continued

Table 4-7g	**Triglyceride** (N = 2065)	
	β (95% CI)	**OR (95% CI)**
Model 1	(continuous)	(> 75th percentile)
PHQ-9 ≥ 10 vs. < 10	**0.10 (0.04, 0.17)***	1.27 (0.99, 1.62)
HIV+ vs. HIV-	**0.19 (0.13, 0.25)***	**1.95 (1.54, 2.48)***
Age (years)	0.0004 (-0.003, 0.004)	1.01 (0.99, 1.02)
Sex	**0.13 (0.01, 0.25)***	1.48 (0.86, 2.55)
White	[Reference]	1.00 [Reference]
Black	**-0.26 (-0.32, -0.19)***	**0.47 (0.36, 0.60)***
Hispanic	-0.03 (-0.14, 0.08)	0.96 (0.65, 1.40)
Other	-0.06 (-0.21, 0.08)	0.91 (0.54, 1.53)

Table 4-7h	**Triglyceride**	
	β (95% CI)	**OR (95% CI)**
Model 2	(continuous)	(> 75th percentile)
PHQ-9 ≥ 10 vs. < 10	**0.08 (0.01, 0.14)***	1.17 (0.91, 1.52)
HIV+ vs. HIV-	**0.28 (0.22, 0.35)***	**2.46 (1.90, 3.20)***
Age (years)	0.001 (-0.002, 0.004)	1.01 (0.99, 1.02)
Sex	**0.12 (0.005, 0.24)***	1.45 (0.84, 2.51)
White	[Reference]	1.00 [Reference]
Black	**-0.27 (-0.33, -0.20)***	**0.44 (0.34, 0.57)***
Hispanic	-0.04 (-0.15, 0.06)	0.92 (0.63, 1.35)
Other	-0.14 (-0.29, 0.005)	0.76 (0.45, 1.29)
Systolic blood pressure	-0.002 (-0.004, 0.001)	1.00 (0.99, 1.01)
Diastolic blood pressure	**0.005 (0.002, 0.009)***	1.02 (1.00, 1.03)
BMI	**0.02 (0.02, 0.03)***	**1.05 (1.03, 1.07)***
Never smoking	[Reference]	1.00 [Reference]
Current	0.002 (-0.07, 0.07)	1.07 (0.81, 1.40)
Past	0.07 (-0.004, 0.15)	1.24 (0.92, 1.66)
HCV infection	0.03 (-0.03, 0.09)	1.11 (0.89, 1.40)
Antidepressant Use	0.02 (-0.04, 0.09)	1.09 (0.86, 1.39)

Table 4-8 Association between MDD and biomarker concentrations by HIV status

	IL-6 (N = 2064)		D-dimer (N = 2070)	
	Model 1	Model 2	Model 1	Model 2
HIV-	**0.17 (0.04, 0.30)***	0.06 (-0.08, 0.20)	0.11 (-0.02, 0.23)	0.003 (-0.13, 0.14)
HIV+	0.006 (-0.08, 0.09)	**-0.10 (-0.19, -0.01)***	0.10 (-0.02, 0.21)	0.02 (-0.11, 0.14)
	sCD14 (N = 2074)		Glucose (N = 2093)	
	Model 1	Model 2	Model 1	Model 2
HIV-	**108.9 (34.9, 182.9)***	25.3 (-55.3, 106.0)	0.007 (-0.04, 0.05)	0.001 (-0.05, 0.05)
HIV+	-15.9 (-77.9, 46.2)	-61. 8 (-129.2, 5.52)	**0.05 (0.02, 0.08)***	0.03 (-0.003, 0.06)
	LDL-c (N = 2035)		HDL-c (N = 2043)	
	Model 1	Model 2	Model 1	Model 2
HIV-	1.68 (-3.84, 7.21)	5.68 (-0.45, 11.8)	1.43 (-0.91, 3.76)	2.08 (-0.47, 4.63)
HIV+	-1.12 (-5.12, 2.88)	1.96 (-2.33, 6.24)	**-2.61 (-4.50, -0.71)***	-1.69 (-3.75, 0.38)
	Triglycerides (N = 2065)			
	Model 1	Model 2		
HIV-	-0.09 (-0.19, 0.003)	-0.07 (-0.18, 0.03)		
HIV+	0.06 (-0.01, 0.13)	0.006 (-0.07, 0.84)		

Model 1: Adjusted for age, sex, and race/ethnicity;

Model 2: Adjusted for age, sex, race/ethnicity, SBP, DBP, BMI, smoking, HCV, and antidepressants

Table 4-9 Association between symptoms of major depression (PHQ-9 ≥ 10) and biomarker concentrations by HIV status

	IL-6		D-dimer	
	Model 1	Model 2	Model 1	Model 2
HIV-	**0.19 (0.05, 0.33)***	0.08 (-0.06, 0.22)	0.02 (-0.11, 0.16)	-0.03 (-0.18, 0.11)
HIV+	0.02 (-0.08, 0.12)	-0.05 (-0.15, 0.05)	0.09 (-0.05, 0.22)	0.03 (-0.11, 0.17)

	sCD14		Glucose	
	Model 1	Model 2	Model 1	Model 2
HIV-	46.8 (-34.8, 128.3)	-16.0 (-99.0, 67.0)	0.02 (-0.03, 0.07)	0.01 (-0.04, 0.06)
HIV+	-9.11 (-81.8, 63.6)	-35.5 (-108.9, 38.0)	-0.01 (-0.05, 0.02)	-0.03 (-0.07, 0.007)

	LDL-c		HDL-c	
	Model 1	Model 2	Model 1	Model 2
HIV-	-5.66 (-11.7, 0.34)	-3.93 (-10.2, 2.31)	0.13 (-2.41, 2.67)	0.67 (-1.93, 3.26)
HIV+	-1.91 (-6.60, 2.77)	-0.16 (-4.83, 4.51)	-1.57 (-3.79, 0.66)	-0.57 (-2.82, 1.68)

	Triglycerides	
	Model 1	Model 2
HIV-	0.06 (-0.04, 0.17)	0.07 (-0.03, 0.18)
HIV+	**0.12 (0.03, 0.20)***	0.08 (-0.008, 0.16)

Model 1: Adjusted for age, sex, and race/ethnicity;

Model 2: Adjusted for age, sex, race/ethnicity, SBP, DBP, BMI, smoking, HCV, and antidepressants

Table 4-10 Supplemental Table. Baseline participant characteristics by HIV status and symptoms of major depression (PHQ-9 ≥ 10) (N = 2,099)

	HIV-uninfected		**HIV-infected**		
Characteristic	**PHQ-9 < 10 (*n* = 546)**	**PHQ-9 ≥ 10 (*n* = 188)**	**PHQ-9 < 10 (*n* = 1097)**	**PHQ-9 ≥ 10 (*n* = 268)**	***P***
Age, years, mean (SD)	54.5 (9.7)	51.7 (7.5)	52.0 (8.1)	51.1 (7.6)	**<.0001**
Male, %	90.8	86.2	96.8	97.8	**<.0001**
African American, %	68.9	59.6	70.9	61.2	
White, %	20.2	24.5	17.9	21.3	**0.0138**
Hispanic, %	6.8	10.6	7.8	12.3	
Other, %	4.2	5.3	3.4	5.2	
BMI, kg/m^2, mean (SD)	29.8 (6.1)	30.6 (7.0)	25.7 (4.9)	26.4 (4.5)	**<.0001**
Systolic BP, mean (SD)	132.3 (14.6)	129.3 (13.7)	128.2 (14.4)	129.1 (14.5)	**<.0001**
Diastolic BP, mean (SD)	78.6 (9.9)	78.3 (9.6)	78.0 (9.0)	79.6 (9.8)	0.0959
Diabetes mellitus, %	38.1	42.6	27.4	25.4	**<.0001**
Statin use, %	14.3	18.6	14.3	13.8	0.4437
Current smoking, %	43.0	63.9	49.0	57.1	
Past, %	28.9	14.2	24.8	23.1	**<.0001**
Never, %	28.0	21.9	26.2	19.8	
Alcohol abuse, %	42.5	57.5	34.8	51.1	**<.0001**
Cocaine use, %	35.0	47.9	31.9	45.2	**<.0001**
HCV infection, %	29.9	41.5	46.7	57.8	**<.0001**

Table 4- 10 Continued

	HIV-uninfected		HIV-infected		
Characteristic	**PHQ-9 < 10 (*n* = 546)**	**PHQ-9 ≥ 10 (*n* = 188)**	**PHQ-9 < 10 (*n* = 1097)**	**PHQ-9 ≥ 10 (*n* = 268)**	***P***
Any antidepressant use, %	21.6	44.2	23.6	44.8	**<.0001**
SSRI use, %	14.5	35.1	14.0	32.5	**<.0001**
TCA use, %	2.9	4.8	5.5	10.8	**<.0001**
Other antidepressant use, %	14.5	32.5	14.6	29.9	**<.0001**
ART use, %	--	--	93.6	94.8	0.2634
HIV-1 RNA, copies/mL, median (IQR)	--	--	75.0 (50.0, 2507.5)	75.0 (50.0, 8274.5)	0.2705
CD4, median (IQR)	--	--	406.0 (264.5, 606.0)	403.0 (245.0, 571.5)	0.2217
CD4 nadir, median (IQR)	--	--	187.0 (70.5, 301.0)	190.0 (85.0, 277.0)	0.7254
CD8, mean (SD)	--	--	969.4 (516.4)	971.6 (509.4)	0.9575
CD4:CD8, median (IQR)	--	--	0.50 (0.30, 0.70)	0.40 (0.30, 0.70)	0.4421

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants

Table 4-11 Supplemental Table 1. Exploring major depressive disorder and treatment; Comparison between major depressive disorder and PHQ-9 Score ≥ 10

	MDD untreated	MDD with antidepressants	No MDD	***Total Sample***
PHQ-9 score ≥ 10, n (%)	111 (19.3)	158 (17.3)	187 (13.2)	***456 (21.7)***
PHQ-9 score < 10, n (%)	196 (80.8)	213 (82.8)	1,234 (86.8)	***1,643 (78.3)***
Total sample	***307 (14.6)***	***371 (17.7)***	***1,421 (67.7)***	***2,099***

Abbreviations: MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire – 9 item

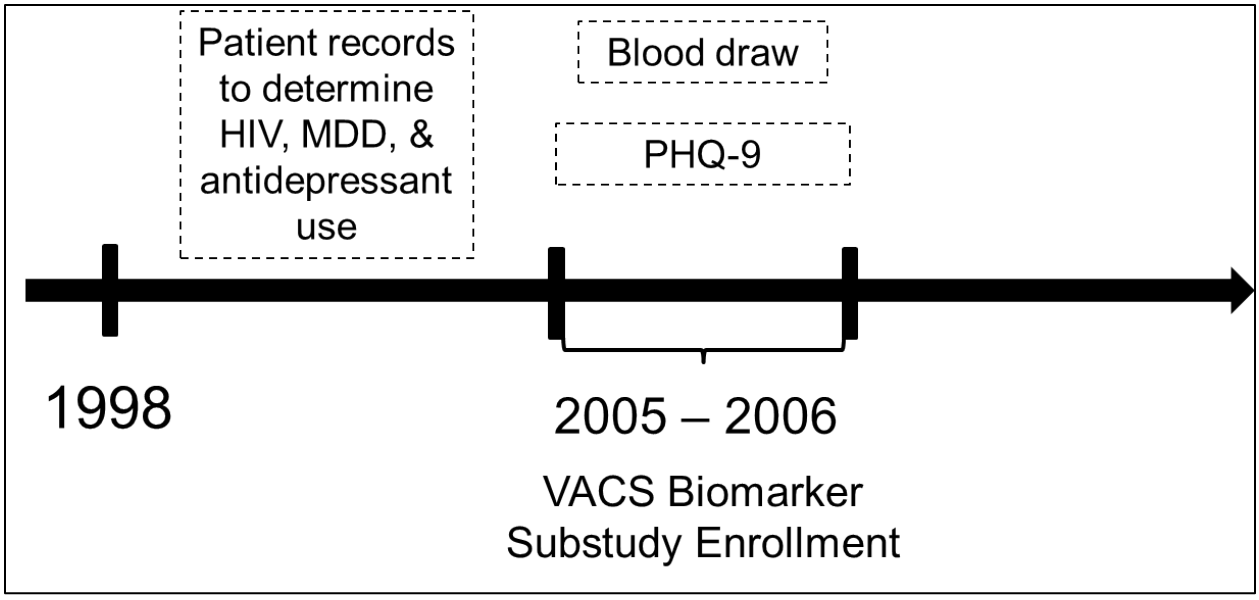

Figure 4-1. Timeline of independent and dependent variables

5.0 BIOMARKER PROFILE ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN VETERANS WITH AND WITHOUT HIV INFECTION

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5.1 ABSTRACT

BACKGROUND: Depressive symptoms are associated with systemic biochemical changes. These changes can be detected by measuring concentrations of growth factors, markers of inflammation, endocrine markers, and metabolic markers in peripheral blood. We provide biomarker profiles associated with depressive symptoms in HIV positive and HIV negative veterans.

METHODS: We analyzed data from participants enrolled in the Veterans Aging Cohort Study (VACS), a large prospective cohort of HIV+ and HIV- veterans matched by age, sex, race/ethnicity, and geographical region. This study included 303 participants from the Three Site Cardiovascular Disease Substudy who completed the nine item Patient Health Questionnaire (PHQ-9). We used linear regression to determine whether self-reported symptoms of major depression, defined as PHQ-9 $\geq$ 10, were associated with decreased growth factor concentration and increased inflammatory markers, endocrine markers, and metabolic markers in both the HIV- and HIV+ participants.

RESULTS: This sample included 63 (20.8%) participants with symptoms of major depression, and there was no significant difference in depressive symptom severity by HIV status. Age and body mass index (BMI) varied significantly across the HIV/depression groups. In HIV- participants, triglyceride concentrations were significantly higher among those with depression compared to those without depression. In HIV+ participants, depression was associated with significantly lower concentrations of VEGF and significantly higher concentrations of leptin. In models adjusted for age, race/ethnicity, and BMI, depression was associated with glucose, LDL-

c, and triglyceride concentrations in HIV- participants, and leptin in HIV+ participants. In exploratory analysis, depression was associated with metabolic syndrome in HIV- participants. CONCLUSIONS: Our study is the first to provide an extensive biomarker profile for individuals with and without depressive symptoms in a cohort of HIV- and HIV+ veterans. We found significant changes in a few metabolic markers with symptoms of major depression and these changes varied by HIV status. Future studies may use these findings to determine whether these biomarkers mediate the association between depression and cardiovascular diseae.

5.2 INTRODUCTION

Depressive symptoms are associated with systemic changes that can be quantified by biomarkers in peripheral blood.[4] Schmidt, *et al*. (2011) identified four sets of biomarkers that warrant further investigation in studies of depression: growth factors, markers of inflammation, endocrine markers, and metabolic markers. Pathological concentrations of these biomarkers are associated with cardiovascular disease (CVD) and death.[87]

HIV infection is also associated with these biomarkers and CVD events.[80] We recently provided evidence that major depressive disorder (MDD) is associated myocardial infarction and heart failure in both HIV negative (HIV-) and HIV positive (HIV+) veterans, and that the risk for incident cardiovascular disease events were highest in those with co-occurring HIV and depression.[74, 75] The mechanisms related to these associations remain unexplained. Yet, it stands to reason, that the altered concentrations of growth factors, cytokines, endocrine markers, and metabolic factors observed with depression may be important for driving the excess cardiovascular risk with co-occurring depression and HIV infection.

We had a unique opportunity to explore biomarker profiles in a cohort of HIV+ and HIV- veterans who reported their depressive symptoms. Our aim was to determine whether depression was associated with changes in concentrations in concentrations of growth factors, cytokines, endocrine markers, and metabolic factors in both HIV+ and HIV- veterans. We hypothesized that symptoms of major depression were associated with (1) lower concentrations of growth factors, (2) higher concentrations of inflammatory makers, (3) higher concentrations of endocrine markers, and (4) higher concentrations of metabolic biomarkers compared to those without symptoms of major depression. We also hypothesized that the biomarker profiles would show different trends in HIV- participants compared to those with HIV infection.

5.3 METHODS

Participants

The Veterans Aging Cohort Study (VACS) is a large prospective study of HIV+ and HIV- veterans who were matched 1:2 by age, sex, race/ethnicity and geographical region during the same enrollment year from the US Department of Veterans Affairs (VA) system. Details about the study participants have been published previously.[50] For this analysis, we used data from the VACS Three Site CVD Study, a subset of over 300 VACS participants who completed a series of questionnaires and provided blood samples for in depth peripheral blood analysis. Participants with acute myocardial infarction, unstable angina, heart failure, stroke or transient ischemic attack, peripheral vascular disease, or cardiovascular revascularization diagnosis on or before their baseline enrollment date were excluded from this analysis. The baseline enrollment period was between 2009 – 2013. These conditions were determined using International

Classification of Diseases, Ninth Revision (ICD-9) codes from their VA medical records. This study was approved by Institutional Review Boards at the University of Pittsburgh, Yale University, and West Haven VA Medical Center and participants provided written informed consent.

Independent Variables

Participants were classified as HIV+ if their medical record included at least one inpatient ICD-9 code for HIV infection and/or at least two outpatient ICD-9 codes for HIV infection at the time of enrollment. This algorithm was developed in the original VACS analyses and has been shown to have high sensitivity (90%), specificity (99.9%), and positive predictive value (88%).[50]

We examined depressive symptoms using the nine-item Patient Health Questionnaire (PHQ-9).[82] The PHQ-9 is a self-report questionnaire that assesses depressive symptoms over the preceding two weeks.[88] Cumulative scores range from 0 (least severe) to 27 (most severe). Using a score of 10 or higher on the PHQ-9, the sensitivity and specificity for the predicting MDD in the primary care population is 74% and 91%, respectively.[83] The PHQ-9 has been validated in HIV+ participants.[89] Since a meaningful PHQ-9 score requires a sum of scores from all nine items, we excluded participants who did complete all of the questions.

Four PHQ-9 score cut-points have been established to classify depression symptom severity. These include: *no major depression* (PHQ-9 < 10); *mild major depression* (PHQ-9 10 – 14); *moderate major depression* (PHQ-9 15 – 19); and *severe major depression* (PHQ-9 $\geq$ 20).

Dependent Variables

Biomarkers included in this study were based on recommendations provided in the review article by Schmidt, *et al*. (2011), which identified key biomarkers for understanding depression physiology.[4] In chapter 4, we analyzed pre-existing laboratory results. In this

smaller and more recent VACS substudy, we were able to analyze a more expansive set of depression-specific biomarkers.

Participant plasma (EDTA) and serum were collected during a clinical visit from 2005 – 2006. Laboratory analyses were conducted at the Laboratory for Clinical Biochemistry Research, University of Vermont.

Growth Factor Vascular endothelial growth factor (VEGF) concentration (pg/mL) was measured from participant serum using a sandwich ELISA (R&D Systems, Inc., USA).

Inflammatory Markers Chemiluminescent sandwich ELISA (R&D Systems, Inc., USA) was used to measure interleukin-6 (IL-6) concentration (pg/mL) in participant serum. Plasma concentrations of tumor necrosis factor-α (TNF- α, pg/mL) were quantified using magnetic bead multiplex with flow-cytometry technique (Millipore Panel B). High sensitivity C-reactive protein (hs-CRP) serum concentrations were measured with the Siemens BNIII Nephelometer.

Endocrine Marker Cortisol concentration (μg/dL), an endocrine marker, was analyzed with electrochemiluminescence immunoassay (Roche Elecys).

Metabolic Markers Serum leptin concentration (pg/mL) was measured using R&D Elisa. Fasting insulin concentration (μU/mL) was measured from participant serum with Roche Elecsys 2010. Metabolic marker concentrations glucose; HDL-c; LDL-c; and triglycerides were obtained from VA outpatient laboratory reports.

Metabolic syndrome was defined using the World Health Organization definition. The criteria requires (i) fasting glucose > 110 mg/dL OR diabetes / medication for diabetes OR insulin resistance; and two of the following: (ii) triglycerides ≥ 150 mg/dL and / or HDL-c < 35 mg/dL; (iii) BMI > 30 kg/m^2; (iv) SBP ≥ 140 mmHg and / or DBP ≥ 90 mm; or (v) microalbuminuria (urine albumin ≥ 20 g/min OR albumin:creatinine ratio ≥ 30 mg/g.

Medication for diabetes, insulin resistance, and measures of microalbuminuria were not available for this analysis. **Figure 5-1** illustrates the timeline of independent and dependent variables.

Covariates

Age, sex, and race/ethnicity were acquired through administrative data. Medical data regarding hypertension, diabetes, serum lipids, renal function, anemia, hepatitis C virus (HCV) infection, and alcohol and cocaine abuse or dependence were obtained from baseline outpatient records, survey question instruments, and laboratory reports. The VA additionally collected health factor data including body mass index (BMI; kg/m^2).

Statistical Analysis

Chi-square analyses were used to compare the frequency of depressive symptom categories by HIV status. Chi-square analyses and ANOVA were used to compare categorical and continuous baseline characteristics across the four HIV / depression groups as appropriate.

In order to compare crude biomarker concentrations by HIV and depression status, we reported means with standard deviations for normally distributed biomarkers (cortisol, HDL-c, and LDL-c) and medians with interquartile ranges for biomarkers that were not normally distributed (VEGF, IL-6, TNF-α, hs-CRP, insulin, glucose, leptin, and triglycerides). Appropriate statistical tests were used to compare mean and median concentrations by depression and across the four HIV / depression groups. For each group, we also reported the proportion of participants with biomarker concentrations in the highest quartile, except for the growth factor, VEGF, where we reported proportions in the lowest quartile. Appropriate statistical tests were used to compare these proportions across groups.

Standard multiple regression models were produced to model the association between depressive symptoms and biomarkers on a continuous scale. Biomarkers that were not normally

distributed were log-transformed. The first model was adjusted for age and race/ethnicity, and a second model added BMI. We explored these models in the entire cohort and by HIV status.

5.4 RESULTS

The final sample included 303 veterans (195 HIV+, 108 HIV-). Symptoms of major depression were common in this sample with 20.8% of the sample having PHQ-9 scores ≥ 10. Mean PHQ-9 scores did not differ significantly between HIV+ and HIV- participants (mean (SD), 4.73 (5.74) and 5.16 (6.13), respectively) and neither did depression symptom severity (**Table 5-1**). Age and BMI varied across the HIV/depression groups (**Table 5-2**). In both HIV- and HIV+ participants, those with depression tended to be younger and have higher BMI.

In those without HIV infection, median VEGF concentration did not differ significantly by depression status, but revealed a trend of being lower with symptoms of major depression (**Table 5-3**). Similarly in those with HIV infection, the median concentration of VEGF was lower in those with depression compared to those without depression and those findings were statistically significant. Concentrations of the three markers of inflammation (IL-6, TNF-α, and hs-CRP) and the endocrine marker (cortisol) were not significantly different by depression status in either HIV group. Insulin, glucose, HDL-c, and LDL-c concentrations were not significantly different by depression status in the HIV+ and HIV- participants. Leptin concentration was higher with depression in the HIV+ participants but not significantly different by depression status in the HIV- participants. Conversely, triglyceride concentration was higher with depression in the HIV- participants but not significantly different by depression status in the HIV+ participants.

Table 5-4 provides the findings from liner regression models stratified by HIV status. In adjusted models, depression was not associated with VEGF, IL-6, TNF-α, hs-CRP, cortisol, insulin, or HDL-c in participants with and without HIV infection. In participants without HIV infection, depression was associated with increased concentrations of glucose and triglycerides and decreased concentrations of LDL-c, after adjusting for age, race/ethnicity, and BMI. In HIV+ participants, depression was associated with increased concentrations of leptin when adjusting for age and race/ethnicity, but the association was no longer significant after including BMI in the model. In models adjusted by age and BMI and stratified by race, depression was associated with decreased concentrations of VEGF in black participants but not in white participants (data not shown).

We explored the association between depression and metabolic syndrome by HIV status. In the HIV- participants, the proportion of those with metabolic syndrome was significantly greater in those with symptoms of major depression (25.0% vs. 2.4%, respectively; $p = 0.0014$). In the HIV+ participants, PHQ-9 scores ≥ 10 were not associated with a significant difference in the proportion of those with metabolic syndrome compared to those with PHQ-9 scores < 10 (15.4% vs. 11.5%, respectively; $p = 0.59$). In an unadjusted logistic regression model, PHQ-9 scores ≥ 10 were associated with metabolic syndrome (**Table 5-5**). The association remained significant when the model was adjusted for HIV, but the association was no longer significant when the model was further adjusted for age and race/ethnicity.

5.5 DISCUSSION

We provide a biomarker profile by depressive symptom severity in HIV+ and HIV- veterans. Depressive symptoms were associated with metabolic marker concentrations, but these trends differed between HIV+ and HIV- participants. The association between the growth factor VEGF and depressive symptoms also varied by HIV status. We did not find significant associations between depressive symptoms and concentrations of markers of inflammation or altered endocrine function in either HIV+ or HIV- participants in this cohort.

VEGF, a molecule that promotes angiogenesis through vascular endothelial cell growth, is also associated with vasodilatation, transient tachycardia, hypotension, and decreased cardiac output in animal models.[90, 91] Recent studies with depression describe mixed findings for VEGF levels. Isung *et al*, reported that both VEGF from cerebral spinal fluid and plasma was associated with both depressive symptoms and suicidal ideation.[92, 93] In a different study, MDD patients had higher expression of VEGF mRNA in peripheral leukocytes compared to those without MDD.[94] We found that median concentrations of VEGF tended to be lower with symptoms of depression, but concentrations were only significantly different in those with HIV infection and the association was lost in models adjusted for age and race/ethnicity.

Large bodies of evidence describe higher concentrations of inflammatory biomarkers among those with either HIV infection or depressive symptoms. In studies comparing HIV+ adults to HIV- adults, hsCRP and IL-6 were higher among those with HIV infection.[95-97] Similarly, depressive symptoms were associated with higher concentrations of TNF-α, IL-6, and IL-1β.[4] Higher concentrations of IL-6 were associated with vascular dysfunction and mortality in a cohorts of HIV+ adults.[98, 99] In this sample, symptoms of major depression were not associated with significant differences in the median concentrations of IL-6, TNF-α, or hs-CRP,

and the adjusted models did not reveal significant associations between depressive symptoms and these markers of inflammation in either HIV group. Our findings are similar, however, to a previous study that found no significant association between depressive symptoms and elevated levels of IL-6 in HIV+ participants.[85] The endocrine marker, cortisol, was not associated with depressive symptoms in this cohort, though we expected a positive association.

The metabolic markers provided the most significant differences with depressive symptoms, and the differences varied by HIV status. In the HIV- participants, there were no significant differences in the concentrations of insulin, glucose, leptin, HDL-c, or LDL-c by symptoms of major depression. Triglyceride concentrations were significantly higher in the HIV- participants with PHQ-9 scores $\geq$ 10 compared to those without symptoms of depression. In adjusted models within the HIV- group, symptoms of major depression were associated with increased concentrations of glucose and triglycerides and decreased concentrations of LDL-c. Crude concentrations of leptin were significantly higher with depressive symptoms in the HIV+ participants, but insulin, glucose, HDL-c, and LDL-c were not significantly different with PHQ-9 scores $\geq$ 10. In the model adjusted for age and race/ethnicity, symptoms of major depression were associated with higher concentrations of leptin, but the association was no longer significant after adding BMI to the model.

Limitations of this study must be addressed. Since this sample was selected from veterans, majority of the participants were men, so findings may not be generalizable to women. Second, the cross-sectional design of this study does not allow us to determine directionality or causality. Prospective studies are required to understand how depressive symptoms and HIV infection influence biomarker concentration changes over time and whether these changes will lead to future cardiovascular disease events. Third, we found in the previous study (Chapter 4 of

this dissertation), that the PHQ-9 score may have misclassification. This definition of depression captures symptoms from the two weeks prior to completing the questionnaire. Scores greater than ten may be due to (i) a transient one time episode of major depression symptoms, (ii) a chronic state of untreated depression, or (iii) or depression that is resistant to antidepressant therapy. On the other hand, scores less than ten may be due to (i) depression that has been effectively managed through therapy or (ii) simply having to rare symptoms of depression. Repeated measures of depression symptom severity and biomarker concentrations would help us understand how these variables are associated. Fourth, and perhaps most importantly, the sample size was small. The trends in **Table 5-3** were quite similar to the trends found in our previous study (Chapter 4, Table 4-5). The findings may not be statistically significant due to inadequate power.

Despite these limitations, our findings provide novel information. This Three Site CVD Substudy allowed us to explore numerous biomarkers in HIV+ and HIV- veterans. It is the first study to describe the biomarker profile of participants with depressive symptoms and HIV infection. Depression in HIV- veterans is physiologically different from depression in HIV+ veterans. The primary mechanisms driving the association between depressive symptoms and cardiovascular disease may differ between individuals with and without HIV infection.

Findings from this study may direct future investigators in conducting mediation analyses to determine physiological mechanisms between depression and CVD in HIV- and HIV+ adults. In order to decrease the risk of CVD from depression, clinicians may need to take different approaches for treating HIV- and HIV+ patients.

5.6 TABLES AND FIGURES

Table 5-1 Depression symptom severity among the total sample and HIV- and HIV+ participants

PHQ-9 Scores	Depression Categorization	Total Sample (N = 303)	HIV- (N = 108)	HIV+ (N = 195)	P value
< 10, n (%)	No major depression	240 (79.2)	84 (77.8)	156 (80.0)	0.6480
10 – 14, n (%)	Mild major depression	32 (10.6)	11 (10.2)	21 (10.8)	0.8741
15 – 19, n (%)	Moderate major depression	24 (7.9)	10 (9.3)	14 (7.2)	0.5209
≥ 20, n (%)	Severe major depression	7 (2.3)	3 (2.8)	4 (2.1)	0.6868

Table 5-2 Baseline participant characteristics by HIV status and symptoms of major depression (PHQ-9 ≥ 10) (N = 303)

	HIV-uninfected		**HIV-infected**		
Characteristic	**PHQ-9 < 10 (*n* = 84)**	**PHQ-9 ≥ 10 (*n* = 24)**	**PHQ-9 < 10 (*n* = 156)**	**PHQ-9 ≥ 10 (*n* = 39)**	**P value**
Age, years, mean (SD)	55.4 (7.1)	53.0 (7.3)	55.0 (7.4)	49.8 (7.2)	**0.0004**
Male, %	100	95.8	99.4	100	0.1499
African American, %	78.6	91.7	78.2	69.2	
White, %	14.3	4.2	15.4	15.4	0.4972
Hispanic, %	4.8	4.2	3.9	12.8	
Other, %	2.4	0.0	2.6	2.6	
Body mass index (kg/m^2), mean (SD)	28.3 (5.1)	29.6 (5.7)	26.3 (6.0)	30.1 (20.2)	**0.0480**
Systolic blood pressure, mean (SD)	129.9 (12.4)	131.2 (13.0)	128.9 (12.6)	128.2 (10.5)	0.7341
Diastolic blood pressure, mean (SD)	78.6 (9.4)	82.7 (7.6)	80.3 (9.0)	81.1 (6.1)	0.1580
Diabetes mellitus, %	17.9	29.2	23.1	20.5	0.6329
Statin, %	25.0	12.5	28.2	28.2	0.4228
Creatinine, mean (SD)	1.04 (0.17)	1.06 (0.21)	1.07 (0.27)	1.04 (0.21)	0.7718
eGFR (mL/min/1.73 m^3), mean (SD)	89.9 (20.0)	91.8 (24.6)	89.7 (25.5)	90.8 (21.3)	0.9761
Hemoglobin, mean (SD)	14.0 (1.2)	14.3 (1.5)	14.0 (1.5)	14.1 (1.3)	0.7753
Current smoking, %	50.0	70.8	50.6	51.3	
Never, %	22.6	12.5	26.3	20.5	0.5539
Past, %	27.4	16.7	23.1	28.2	
Alcohol abuse, %	63.1	79.2	50.0	61.5	**0.0230**
Cocaine abuse, %	54.8	70.8	46.8	51.3	0.1490
HCV infection, %	42.9	58.3	55.8	51.3	0.2520

Table 5-2 Continued

	HIV-uninfected		HIV-infected		
Characteristic	**PHQ-9 < 10 (*n* = 84)**	**PHQ-9 ≥ 10 (*n* = 24)**	**PHQ-9 < 10 (*n* = 156)**	**PHQ-9 ≥ 10 (*n* = 39)**	**P value**
Antiretroviral therapy use, %	--	--	95.5	97.4	0.5881
HIV RNA (copies/mL), mean (SD)	--	--	2,410.5 (8863)	11,607.2 (39041.3)	0.1518
CD4+ count (count/µL), mean (SD)	--	--	494.9 (268.3)	532.9 (234.3)	0.4191
CD4 nadir value, mean (SD)	--	--	212.2 (169.1)	240.7 (120.1)	0.2292
CD8 Lab Results, mean (SD)	--	--	893.3 (379.1)	1012.5 (596.9)	0.2408
CD4:CD8 ratio, mean (SD)	--	--	0.68 (0.64)	0.64 (0.39)	0.5806

Abbreviations: eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein

Table 5-3 Biomarker profiles by HIV status and symptoms of major depression (PHQ-9 ≥ 10) (N = 303)

			HIV-uninfected		P for	HIV-infected		P for	P for
	Biomarker		**PHQ-9 < 10 (*n* = 84)**	**PHQ-9 ≥ 10 (*n* = 24)**	**HIV-**	**PHQ-9 < 10 (*n* = 156)**	**PHQ-9 ≥ 10 (*n* = 39)**	**HIV+**	**trend**
Growth Factor	VEGF (pg/mL)	N = 239	N = 75	N = 15		N = 120	N = 29		
		Median (IQR)	42.1 (24.1, 64.8)	40.9 (32.0, 55.7)	0.9655	37.3 (27.7, 63.4)	27.8 (24.5, 38.0)	**0.0241***	0.1755
		≤ 25th percentile	29.3%	13.3%	0.3374	21.7%	34.5%	0.1479	0.2692
Cytokines / Markers of Inflammation	IL-6 (pg/mL)	N = 240	N = 74	N = 15		N = 121	N = 30		
		Median (IQR)	3.2 (2.0, 5.2)	3.7 (2.3, 4.2)	0.8522	2.8 (1.8, 4.5)	2.8 (1.5, 5.0)	0.9275	0.5240
		> 75th percentile	29.7%	20.0%	0.5426	22.3	26.7%	0.6130	0.6610
	TNF-α (pg/mL)	N = 238	N = 73	N = 15		N = 121	N = 29		
		Median (IQR)	3.0 (2.2, 4.2)	2.7 (2.3, 3.6)	0.6571	3.2 (2.5, 4.4)	3.0 (2.3, 4.2)	0.6332	0.3988
		> 75th percentile	23.3%	6.7%	0.2889	28.1%	24.1%	0.6673	0.3275
	hs-CRP (ug/mL)	N = 210	N = 68	N = 12		N = 105	N = 25		
		Median (IQR)	1.7 (0.85, 3.9)	2.4 (0.35, 6.1)	0.9409	2.1 (0.95, 3.7)	1.3 (0.69, 4.1)	0.3522	0.7952
		> 75th percentile	25.0%	41.7%	0.2950	22.9%	24.0%	0.9030	0.5611
Endocrine Marker	Cortisol (ug/dL)	N = 237	N = 75	N = 15		N = 117	N = 30		
		Mean (SD)	15.2 (5.7)	16.6 (6.5)	0.3960	16.2 (6.3)	14.4 (3.8)	0.0531	0.3685
		> 75th percentile	28.0%	40.0%	0.3683	25.6%	10.0%	0.0670	0.1258
Metabolic Markers	Insulin (uU/mL)	N = 168	N = 45	N = 12		N = 91	N = 20		
		Median (IQR)	11.6 (6.7, 16.0)	11.7 (9.4, 34.0)	0.1502	9.9 (5.5, 14.7)	8.7 (6.1, 17.7)	0.9511	0.1991
		> 75th percentile	24.4%	41.7%	0.2865	22.0%	30.0%	0.5598	0.4762
	Glucose (mg/dL)	N = 301	N = 82	N = 24		N = 156	N = 39		
		Median (IQR)	102.0 (90.0, 112.0)	106.0 (101.5, 129.5)	0.0837	100.0 (90.0, 118.5)	101.0 (93.0, 108.0)	0.9040	0.3075
		> 75th percentile	22.0%	33.3%	0.2543	27.6%	15.4%	0.1168	0.2871
	Leptin (pg/mL)	N = 211	N = 69	N = 13		N = 103	N = 26		
		Median (IQR)	7747.6 (5452.2, 15404.3)	14637.8 (10226.2, 21564.5)	0.1743	6145.7 (2997.5, 11595.0)	10221.4 (4608.3, 15505.0)	**0.0388***	**0.0030***
		> 75th percentile	30.4%	46.2%	0.3377	18.5%	26.9%	0.3357	0.0866
	HDL-c (mg/dL)	N = 301	N = 82	N = 24		N = 156	N = 39		
		Mean (SD)	48.3 (18.6)	43.8 (13.1)	0.2668	43.5 (14.5)	40.8 (15.1)	0.3058	0.0554
		> 75th percentile	26.8%	29.2%	0.8213	21.8%	18.0%	0.5980	0.6023

Table 5-3 Continued

			HIV-uninfected		P for	HIV-infected		P for	P for
	Biomarker		**PHQ-9 < 10 (*n* = 84)**	**PHQ-9 ≥ 10 (*n* = 24)**	**HIV-**	**PHQ-9 < 10 (*n* = 156)**	**PHQ-9 ≥ 10 (*n* = 39)**	**HIV+**	**trend**
	LDL-c (mg/dL)	N = 301	N = 82	N = 24		N = 156	N = 39		
		Mean (SD)	105.4 (29.9)	92.2 (30.0)	0.0606	97.6 (28.0)	103.6 (26.8)	0.2265	0.0948
		> 75th percentile	26.8%	12.5%	0.1458	24.4%	30.8%	0.4122	0.4108
	Triglycerides (mg/dL)	N =	N = 82	N = 24		N = 156	N = 39		
		Median (IQR)	92.0 (70.0, 144.0)	128.0 (85.0)	**0.0197***	119.1 (91.5, 206.0)	125.0 (96.5, 178.0)	0.8058	**0.0017***
		> 75th percentile	13.4%	37.5%	**0.0120***	28.9%	23.1%	0.4714	**0.0261***

Abbreviations: HDL-c, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IL-6, interleukin-6; LDL-c, low-density lipoprotein cholesterol; MDD, major depressive disorder; sCD14, soluble CD14.

Table 5-4 Association between symptoms of major depression (PHQ-9 ≥ 10) biomarkers, β (95% CI)

	VEGF		IL-6		TNF-α	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Total	-0.17	-0.17	0.10	0.10	-0.04	-0.03
cohort	(-0.39, 0.04)	(-0.38, 0.04)	(-0.17, 0.38)	(-0.18, 0.38)	(-0.25, 0.17)	(-0.25, 0.18)
HIV-	-0.11	-0.12	0.16	0.10	-0.04	-0.02
	(-0.53, 0.31)	(-0.55, 0.31)	(-0.26, 0.58)	(-0.32, 0.51)	(-0.40, 0.33)	(-0.40, 0.36)
HIV+	**-0.21**	-0.20	0.10	0.12	-0.01	-0.006
	(-0.45, 0.04) †	(-0.45, 0.04)	(-0.27, 0.47)	(-0.26, 0.50)	(-0.28, 0.26)	(-0.27, 0.26)

	hs-CRP		Cortisol		Insulin	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Total	-0.24	-0.31	-0.42	-0.14	0.28	0.24
cohort	(-0.69, 0.21)	(-0.76, 0.15)	(-2.39, 1.55)	(-2.12, 1.84)	(-0.06, 0.62)	(-0.11, 0.58)
HIV-	-0.08	-0.26	1.65	1.97	0.53†	0.43
	(-0.92, 0.76)	(-1.09, 0.57)	(-1.66, 4.97)	(-1.33, 5.28)	(-0.07, 1.13)	(-0.14, 1.01)
HIV+	-0.30	-0.35	-1.79	-1.58	0.10	0.05
	(-0.83, 0.24)	(-0.90, 0.20)	(-4.29, 0.72)	(-4.13, 0.97)	(-0.33, 0.53)	(-0.38, 0.49)

Model 1: age and race/ethnicity;

Model 2: age, race/ethnicity, and BMI

*P < 0.05; † P < 0.10

Table 5-4 Continued

	Glucose		Leptin		HDL-c	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Total	0.05	0.04	**0.39***	0.23	-2.29	-2.01
cohort	(-0.03, 0.13)	(-0.04, 0.11)	**(0.08, 0.70)**	(-0.06, 0.52)	(-7.42, 1.60)	(-6.48, 2.47)
HIV-	**0.12***	**0.12***	0.35	0.14	-4.47	-2.94
	(0.004, 0.24)	**(0.002, 0.24)**	(-0.14, 0.84)	(-0.22, 0.50)	(-12.5, 3.60)	(-10.5, 4.63)
HIV+	0.004	-0.02	**0.45***	0.27	-2.59	-1.73
	(-0.10, 0.11)	(-0.12, 0.09)	**(0.04, 0.86)**	(-0.12, 0.65)	(-8.00, 2.83)	(-7.15, 3.69)

	LDL-c		Triglycerides	
	Model 1	Model 2	Model 1	Model 2
Total	-2.98	-3.08	0.12	0.11
cohort	(-11.1, 5.16)	(-11.3, 5.14)	(-0.06, 0.29)	(-0.07, 0.29)
HIV-	**-16.4***	**-17.4***	**0.40***	**0.39***
	(-30.1, -2.67)	**(-31.1, -3.75)**	**(0.11, 0.69)**	**(0.10, 0.68)**
HIV+	4.51	4.88	-0.04	-0.05
	(-5.51, 14.5)	(-5.27, 15.0)	(-0.26, 0.18)	(-0.28, 0.18)

Model 1: age and race/ethnicity;

Model 2: age, race/ethnicity, and BMI

*P < 0.05; † P < 0.10

Table 5-5 Logistic regression models between symptoms of major depression and metabolic syndrome

	Model 1		Model 2		Model 3	
Characteristic	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
PHQ-9 ≥ 10 vs. < 10	2.59	(1.19, 5.63)	2.65	(1.21, 5.81)	2.73	(0.82, 4.90)
HIV+ vs. HIV-	--	--	1.82	(0.78, 4.25)	1.88	(0.82, 5.50)
Age (per 10 years)	--	--	--	--	1.00	(0.94, 1.05)
White	--	--	--	--	1.00	[Reference]
African American	--	--	--	--	2.60	(0.59, 11.5)
Hispanic	--	--	--	--	2.36	(0.29, 19.3)
Other	--	--	--	--	8.89	(0.97, 81.5)

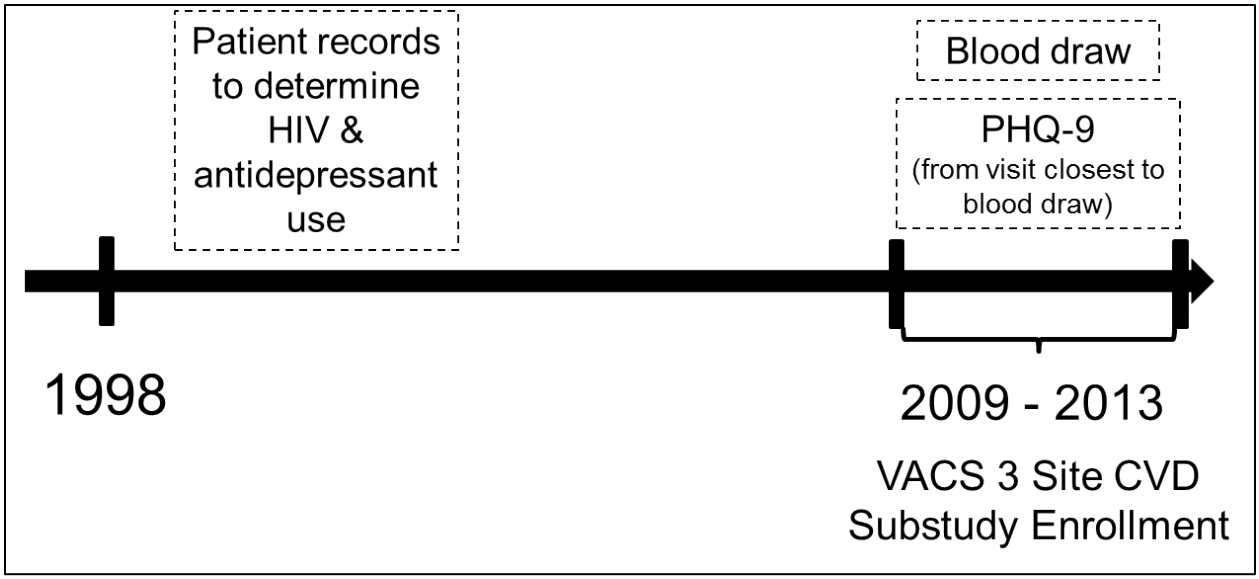

Figure 5-1. Timeline of independent and dependent variables

6.0 DISSERTATION DISCUSSION

6.1 MAJOR FINDINGS

This dissertation provides new and important information about cardiovascular disease (CVD) outcomes and physiology of adults with co-occurring depression and HIV infection. First, using data from over 80,000 veterans enrolled in the Veterans Aging Cohort Study, we found that HIV infection and major depressive disorder (MDD) are each associated with an increased risk of incident HF. Participants with co-occurring HIV infection and MDD had the highest rates and risk of incident heart failure compared to participants with only one these conditions or neither condition. These findings were robust. In an analysis restricted to HIV+ participants, MDD was associated with incident heart failure, even after adjusting for HIV severity. As an exploratory analysis we found that among those with MDD, baseline antidepressant use was associated with lower risk of incident HF events. This study is the first to suggest MDD is an independent risk factor for HF in HIV+ adults.

Understanding that depression and HIV pathophysiology overlap, we explored biomarker concentrations in two cohorts. In a sample of 2,099 participants, MDD was associated with glucose concentrations in the highest quartile and PHQ-9 scores $\geq$ 10 were associated with higher triglyceride concentrations. In models restricted by HIV status and adjusted for age, sex, and race/ethnicity, MDD was associated with increased concentrations of IL-6 and sCD14 in the

HIV- participants and associated with increased concentrations of glucose and decreased concentrations of HDL-c in the HIV+ participants. In a smaller sample of 309 veterans, depression was associated with glucose, LDL-c, and triglyceride concentrations in HIV- participants, and leptin in HIV+ participants. We hypothesized that co-occurring HIV infection and depression would result in excessive inflammation, coagulation, monocyte activation, and endocrine response, altered metabolism, and depleted growth factor. In both of these samples, we found that depression was associated with altered concentrations of biomarkers, and that the changes observed in the HIV- participants were different from the changes observed in the HIV+ participants; but our findings did not support our hypotheses. These findings indicate that the physiological pathways mediating depression and cardiovascular disease may differ with co-occurring HIV infection.

6.2 PUBLIC HEALTH SIGNIFICANCE

Our health depends on the exposures we face across the lifecourse and how well our bodies adapt to these exposures. Public health investigators aim to (i) discover the specific exposures that impact our health in positive and negative ways; (ii) determine which traits are associated with being healthy or ill; and (iii) provide evidence-based solutions for achieving a healthy state. Understandably, the field of public health is vast and requires experts that range from geneticists to environmental epidemiologists. As it is impossible to become an expert in all things, we as public health investigators often specialize in a specific organ system or pathogen (e.g. traumatic brain injury or influenza). We must remember to seek literature outside our field of expertise and consider how discoveries from other disciplines may impact our own findings. This

dissertation illustrates the significance of asking cross-cutting, multi-disciplinary public health questions.

The idea for this dissertation stemmed from my interest in infectious diseases. As I explored the HIV literature, I discovered studies that provided hypotheses for the significant association between HIV infection and increased risk of cardiovascular disease. During a seminar lecture, I learned about a second non-traditional risk factor for cardiovascular disease, i.e. depression. The hypotheses to describe the pathophysiological mechanisms between HIV and CVD and between depression and CVD seemed to overlap. I developed specific aims that incorporated findings from these three disciplines. As a result, this dissertation provides evidence that a mental health condition (depression) is a significant predictor of short-term physiological changes (biomarkers) and chronic disease risk (heart failure) in individuals with an infectious disease (HIV).

The findings from this cross-cutting dissertation have many clinical implications and provide numerous new avenues for further investigation. Now that we know that depressive symptoms contribute to the burden of CVD among individuals with HIV, we must advocate for comprehensive healthcare. HIV+ patients should be systematically screened for affective disorders. To address symptoms of depression and their implications with cardiovascular disease, clinicians may need to consider different interventions depending on the HIV status of their patients.

6.3 FUTURE DIRECTIONS

This dissertation is hypothesis generating and provides many opportunities for future analysis. Using the knowledge gained in Chapter 3, we now understand that co-occurring HIV infection and MDD leads to increased risk of heart failure (HF). To further understand the etiology associated with this heart failure risk, we could analyze ejection fraction data and explain whether the HF is systolic or diastolic. We could look at other CVD events, such as stroke or CVD mortality, and determine whether co-occurring HIV and depression also increases these risks. Additionally, we could explore subclinical changes that occur before a CVD event. For example, we could look at structural changes, such as intima-media thickness or coronary artery calcification, and functional changes, such as endothelial function or stress test performance.

We used two definitions for depression, which classified participants as “depressed” or “not depressed” at a single time point. To address the limitations related to this cross-sectional variable, we could study depression using repeated measures. This prospective approach would help us understand how biomarker concentrations and CVD risk are impacted by transient episodes and chronic states of depression. It would also be important to further understand how antidepressant use affects depressive symptoms, biomarker concentrations, and long-term outcomes. A randomized controlled trial would help us understand whether effective management of depression reduces CVD risk in HIV+ and HIV- participants.

Finally, depression and HIV infection are just single examples of an affective disorder and a chronic inflammatory condition. We could explore CVD risk with any combination of mental health conditions and inflammatory conditions, with their respective therapies. Examples include anxiety and systemic lupus erythematosus or post-traumatic stress disorder and rheumatoid arthritis. Epidemiologists have many options with these multi-disciplinary studies.

APPENDIX A: LITERATURE REVIEW SUMMARY TABLES: HEART FAILURE

Table 6-1 Summary of literature: Depression and heart failure

				Study participants						
Author (year)	N	Measurement of depression	Outcome	Follow-up	Age (years)	Male (%)	White (%)	Important inclusions	Measure of Association	Key findings
Whooley (1998)[47]	7518	GDS-SF ≥ 6	Congestive HF mortality based on adjudicated hospital records and death certificates	Mean 6 years	Mean 72	0.00	100	Elderly	HR = 3.2 (1.3 - 8.0)	Depressive symptoms associated with mortality from congestive heart failure
Chen (1999)[14]	1749	CES-D ≥ 16	Incident HF based on hospitalization records	Mean 7.9 years	Mean 77.8	41.1	79.5	Elderly of Connecticut	RR = 1.10 (p = 0.65)	Depression was not independently associated w/ incidence of HF
Abramson (2001)[11]	4538	CES-D ≥ 16 at baseline	Incident HF based on adjudicated diagnosis from medical records	Mean 4.5 years	Mean 71.6	44.2	86.8	Elderly w/ isolated systolic hypertension	HR = 2.59 (1.57 - 4.27)	Depression was a significant risk of HF even after adjusting for MI
Williams (2002)[12]	2501	CES-D ≥ 21 at baseline	Incident HF based on review of hospital records, death certificates, and medicine bottles	14 years	Mean 74	41.9	Pre-dominantly	YHAP cohort	♀ HR = 1.96 (1.11 - 3.26) ♂ HR = 0.62 (0.23 - 1.71)	Depression was a significant risk in women, but not in men or in the combined cohort
Bremmer (2006)[15]	2403	DSM-III Criteria for Major Depressive Disorder; Sub-threshold depression defined as CES-D ≥ 16 w/o diagnosis	Incident HF based on self-report of symptoms, medications, or previous diagnosis; Lumped with arrhythmia into "Non-ischemic CVD" group	Mean 7.2 years	Mean 69.4	45.7	Not provided	The Netherlands; LASA cohort	RR = 0.96 (0.24 - 3.89) for MDD	Neither major depression or subthreshold depression were significant predictors of Non-ischemic CVD even after adjusting for age and sex
Vaccarino (2007)[13]	559	BDI < 10 & no history of depression BDI ≥ 10 OR history of depression BDI ≥ 10 AND history of depression	Exploratory analysis conducted on HF due to few events IL-6 and CRP	Median 5.9 years	Approx 58	0.00		Women suspected of coronary ischemia; WISE cohort	Trend across categories were significant for CRP (p < 0.0001) and IL-6 (p = 0.0008)	Exploratory analysis found significant risk of HF (HR not provided) IL-6 and CRP explained only some of the association with CVD

Table 6-1 Continued

Donath (2010)[10]	30	DSM-IV criteria for Major Depressive Disorder based on a Structured Clinical Interview; BDI & HAM-D 21 to assess severity	Respiratory gas exchange endpoints including oxygen uptake, carbon dioxide output, and ventilation		Mean 38	0.00		Controls matched on age, BMI, and physical activity	Inverse relationship between VE/VCO_2 slope and MDD (p = 0.0012)	Depressed women had decreased ventilatory efficiency
Kop (2010)[17]	870	CES-D ≥ 8 at baseline	Fibrosis markers: Procollagen type I (PIP); Type I collagen (CITP); & Procollagen type III (PIIINP)		Mean 80.4	51.0	Not provided	Elderly; CHS cohort; Non-random sample; Case-control study based on HF status	Depression and PIP: Adjusted OR = 1.43 (1.00-2.03)	Depression was associated with Procollagen type I even after adjustment for CRP, WBC, and fibrinogen
Kim (2012)[16]	2420	No depression: 0 ≤ BDI < 10 Mild depression: 10 ≤ BDI < 20 Moderate - severe depression: BDI ≥ 20	Subclinical LV changes based on echocardiography and tissue Doppler imaging	Cross-sectional	Approx 57	48.6	Not provided	Korean Genome Epidemiology Study	Higher LV mass index (p = 0.019) and lower TDI E_a velocity (p = 0.006) with moderate to severe depression	Depression was associated with subclinical changes to the LV in structure and function
Garfield (2014) [100]	236079	MDD; ICD-9-CM codes in VHA records	Incident HF; ICD-9-CM in VHA records	Prospective	Mean 62.8	93.4	78.7	VA patients; free of CVD; age 50 – 80	Adjusting for CVD risk factors & substance abuse HR = 1.11 (1.04-1.18)	MDD, anxiety, and MDD/anxiety were each associated with higher risk of incident HF
Gustad (2014) [101]	62567	Self-reported depressive symptoms Hospital Anxiety & Depression Scale (HADS)	Incident HF; linkage w/ medical records or by the National Cause of Death Registry	Prospective	Approx 66	46.9	Not provided	HUNT 2 study; Norway	For moderate symptoms: HR = 1.07 (0.87-1.30) For severe symptoms: HR = 1.41 (1.07-1.87)	Symptoms of depression were associated w/ increased risk of HF in a dose-response manner; anxiety not associated
Loomba (2015) [102] [Epub ahead of print]	> 2700	Patients feeling down/ depressed/ hopeless divided into 2 categories: symptoms more than half the days of the week & those with less frequent symptoms	Prevalence of CHF	Cross-sectional	> 45			2007-2008 NHANES data	OR = 2.54 (1.61-4.01)	Those who reported being depressed more than half of the days of the week had higher odds of CHF compared to those who reported being depressed less often

Table 6-2 Summary of literature: HIV and heart failure

		Study participants								
Author (year)	N	Measurement of HIV	Outcome	Follow-up	Age (years)	Male (%)	White (%)	Important inclusions	Measure of Association	Key findings
Cardoso (1998)[39]	138	HIV diagnosis from clinic	Left ventricular function by echocardiography	Cross-sectional	Mean 34	68.1		Portugal clinic patients	HIV+ compared to HIV-: ↑ LV diastolic diameter ↑ LV systolic diameter ↓ LV fractional shortening ↓ LV ejection fraction ↑ isovolumetric relaxation time ($p < 0.0005$ for all)	HIV+ had significantly poorer heart function compared to HIV-
Schuster (2008)[40]	56	HIV+ receiving HAART for ≥ 2 years vs. healthy controls	Cardiac function based on echocardiography		Approx 41	100	100	France	HIV+ compared to HIV-: ↑ Septal wall thickness ↑ LV diameter ↑ LV systolic diameter ↓ Cardiac index ↓ Peak systolic velocity tissue ($p < 0.01$ for all)	HIV+ had significantly poorer heart function compared to HIV-
Lai (2009)[41]	46	HIV confirmed by Western blot	Tagged MRI: Regional left ventricular myocardial mid-wall peak systolic circumferential strain (Ecc) & early diastolic strain rate (SRE) of LV by harmonic phase analysis	Cross-sectional	Mean 40	60.9	0	Asymptomatic of CVD	HIV+ compared to HIV-: 3/16 Ecc segments were significantly less 6/16 Ecc segments were significantly less	HIV+ was associated with regional LV dysfunction compared to HIV-
Hsue (2010)[42]	242	Medical records, letter of diagnosis, or HIV-antibody testing	Left ventricular ejection fraction Left ventricular mass indexed to body surface area (LVMI) Diastolic function		Approx 46		71.9	SCOPE; San Francisco, CA	Adjusted ORs: diastolic dysfunction OR = 2.4 (1.2 - 4.7); LV Mass Index OR = 9.4 (4.8 - 14.0)	HIV was associated with higher prevalence of diastolic dysfunction and higher LVMI

Table 6-2 Continued

Study participants										
Author (year)	N	Measurement of HIV	Outcome	Follow-up	Age (years)	Male (%)	White (%)	Important inclusions	Measure of Association	Key findings
Butt (2011)[25]	8486	1 or more inpatient and/or 2 or more outpatient ICD-9 codes for HIV infection	1 or more inpatient and/or 2 or more outpatient ICD-9 codes for HF	Median 7.3 years	Median 48.0		Approx. 40	VACS-VC Cohort	Adjusted HR: 1.81 (1.39 - 2.36)	HIV infection is associated with a significant risk of HF; the association is significant when baseline HIV-1 RNA level ≥ 500 copies / mL, but not when below this level
Grandi (2012)[103]	120	HIV^+ hypertensives HIV^+ normotenstives HIV^- hypertensives HIV^- normotensives	Based on echocardiogram: LV diatmeter; interventricular septum thickness; LV posterior wall thickness; relative wall thickness; LV mass; LV ejection fraction		Approx 45	86.6		Clinic cases and controls	HIV^+ hypertensives: 51.5 g HIV^+ normotenstives: 42.8 g HIV^- hypertensives: 44.5 g HIV^- normotensives: 36.3 g ANOVA, significant	HIV^+ hypertensives had greater LV mass and preclinical diastolic dysfunction compared to HIV^- hypertensives HIV^+ normotensives had greater LV mass and lower LV diastolic indices compared to HIV^- normotensives

Table 6-2 Continued

				Study participants						
Author (year)	N	Measurement of HIV	Outcome	Follow-up	Age (years)	Male (%)	White (%)	Important inclusions	Measure of Association	Key findings
Oramas-ionwu (2012)	1.5 mil hospital discharges in African American & white w/ HIV/AIDS; 288 mil w/o HIV/AIDS	HIV / AIDS ICD-9-CM codes	HF-related hospitalization based on ICD-9-CM codes					NHDS national hospitalization records	Afr Am w/ HIV/AIDS: 34% Afr Am, uninfected: 28% White w/ HIV/AIDS: 25% White, uninfected: 23%	Africans Americans & whites w/ HIV/AIDS had greater proportion of HF hospitalization compared to uninfected African Americans w/ HIV > proportion than whites w/ HIV
Womack (2015)	2187	HIV	1 inpatient / 2 or more outpatient ICD-9-CM for HF	6.0	Mean Approx 43	0	Approx 30	VACS; women free of CVD	Incidence rate ratio = 2.5 (1.5-4.5)	HIV was associated with increased risk of HF in women

Abbreviations: AIDS, acquired immune deficiency syndrome; HF, heart failure; HIV, human immunodeficiency virus; HR, hazard ratio; ICD-9-CM, The International Classification of Diseases, 9th Revision, Clinical Modification; LHS, Large Health Study of Veteran Enrollees; LV, left ventricle; MRI, magnetic resonance imaging; NHDS, United States National Hospital Discharge Surveys; SCOPE, Study of the Consequences of the Protease Inhibitor Era; VACS-VC, Veterans Aging Cohort Study – Virtual Cohort

APPENDIX B: LITERATURE REVIEW SUMMARY TABLES: BIOMARKERS

Table 6-3 Summary of Literature: Depression, HIV, biomarkers, and cardiovascular disease

Study participants						
Author (year)	N	Age (years)	Important inclusions	Exposure	Outcome	Key findings
VEGF – Vascular endothelial growth factor – is a protein that stimulates angiogenesis. Peripheral VEGF is measured from plasma collected in EDTA. Reference range: 31 – 86 pg/mL [104]						
Ventriglia et al (2009)[105]	25		Drug-free pts	Depressed in- and outpts & controls	Serum VEGF	No significant differences
Kahl et al (2009)[106]	12		Drug-free pts	Depressed vs. controls; Borderline personality	Serum VEGF	Elevated VEGF in depressed pts
Lee & Kim (2012)[107]	35		Drug-free pts	Moderate depression & acute episodes of depression	Plasma VEGF	Increased plasma VEGF levels in depressed
Clark-Raymond et al (2014)[108]				MDD subjects prior to treatment vs. healthy controls	Plasma VEGF	VEGF higher with MDD
Elfving et al (2014)[109]	435		Danish PRISME study	Depression (ICD-10) vs. healthy, no affective disorders	Serum VEGF	Increased serum VEGF levels in the depressive subjects vs. controls
Taimeh et al (2013)[87]		*Review article*		VEGF	HF	Reduced VEGF in models of advanced HF
Kaidaniuk et al (2011)[110]		*Review article*		VEGF	CVD	Angiogenesis plays a protective role in ischemic heart disease & MI Extends life for pts after stroke
IL-6 – Interleukin-6 – is a cytokine with pro-inflammatory and anti-inflammatory effects. IL-6 is measured in serum and helps to identify inflammatory conditions. Reference range: < 17.4 pg/mL [104, 111]						
Howren et al (2009)[76]	62 studies	N/A	Meta-analysis	Depressive symptoms	IL-6	Circulating peripheral IL-6 was significantly associated with diagnosis of major depression

Table 6-3 Continued

Study participants						
Author (year)	N	Age (years)	Important inclusions	Exposure	Outcome	Key findings
Dowlati et al (2010)[1]	9 studies	N/A	Meta-analysis of studies measuring cytokine concentration in pts w/ major depression	Major depression (DSM criteria)	IL-6	IL-6 concentrations were significantly higher in depressed subjects compared to controls ($p < .00001$)
Fumaz et al (2012)[85]	50	Median: 39.0	HIV-1 infected individuals on effective cART	Psychological stress (Perceived Stress Scale; PSS-10) Anxiety & Depression (Hospital Anxiety & Depression scale; HADS)	IL-6	Strong correlation between IL-6 & psychological stress ($r = .81$) Anxiety / depression were associated with higher levels of IL-6; association not significant in models adjusted by age
Vaccarino et al (2007)[13]	559	Mean: between 53.9 – 59.2	Women w/ suspected coronary ischemia	Depression: (BDI ≥ 10 & diagnosis of depression) Possible depression: (BDI ≥ 10 OR diagnosis of depression) No depression	CVD events (hospital stays for nonfatal MI, stroke, congestive heart failure, and CVD-related death) Possible mediators: CRP & IL-6	Depression associated with 25% higher IL-6 ($p = 0.04$) Possible depression associated with 28% higher IL-6 ($p = 0.01$) Depression was a significant predictor of CVD (HR 2.58, $p = 0.0009$) Possible depression was not a significant predictor of CVD (HR 1.12, $p = 0.68$) Addition of IL-6 decreased estimate for depression by 4% Inflammatory biomarkers explain only a small proportion of the association between depression and CVD incidence
Neuhaus et al (2010)[95]	5880 & 3518	45 – 77 & 33 – 44	SMART study / MESA & SMART study / CARDIA	HIV	IL-6	IL-6 levels were 152% higher ($p < .001$) among HIV-infected participants compared with levels in MESA study participants IL-6 levels were 62% ($p < .001$) higher among HIV-infected participants than among CARDIA participants

Table 6-3 Continued

Study participants						
Author (year)	N	Age (years)	Important inclusions	Exposure	Outcome	Key findings
Armah et al (2012)[80]	2368	Mean: between 51.8 – 53.5	People in the Veterans Aging Cohort Study (VACS)	HIV	IL-6 (>75th percentile)	HIV+ veterans with HIV-RNA ≥ 500 copies/mL had a significantly higher prevalence of elevated IL-6; OR = 1.54; 95% CI, 1.14 – 2.09) HIV+ veterans with CD4 count <200 cells/µL had a significantly higher prevalence of elevated IL-6; OR = 2.25; 95% CI, 1.60 – 3.16)
Orus et al (2000) [112]	87	Mean: 57	CHF patients	Cytokines Il-6, IL-1β, TNF-α, IL-2-sR	Death, new HF episodes, & need for heart transplantation	Increased IL-6 was a predictor of the combined outcome: death, new HF episodes, & need for heart transplantation
Duprez et al (2012)[113]	5098	Mean: between 49.8 – 56.3	HIV patients enrolled in the SMART study	IL-6	CVD (CVD death, non-fatal MI, non-fatal stroke, congestive HF, coronary revascularization, CAD requiring drug treatment, and peripheral artery disease)	Adjusted HR for CVD Q4 vs Q1: 4.65 (2.61, 8.29)
TNF-α – Tumor Necrosis Factor - alpha – is an acute phase reactant that is detectable during systemic inflammation. TNF-α is measured in serum. Reference range: < 5.6 pg/mL[104]						
Dowlati et al (2010)[1]	13 studies		Meta-analysis of studies measuring cytokine concentration in pts w/ major depression	Major depression (DSM criteria)	TNF-α	TNF-α was increased in depressed subjects compared to controls (p < .00001)
Kupper, Widdershoven, & Pedersen (2012) [114]	110 - 125	Mean: Approx. 66	HF patients (Netherlands)	BDI-I	Cross-sectional & prospective cytokines sTNFR1 & 2, IL-1ra, IL-6, CRP	Cognitive/affective depressive symptoms were associated with sTNFR1 & sTNFR2 prospectively Somatic/affective depressive symptoms were associated with sTNFR2 prospectively
Rauchhaus et al (2000)[115]	152	Mean: 61	CHF patients	TNF-α, sTNFR1 & 2, IL-6, sCD14	Mortality (mean follow-up time = 34 months)	sTNF-R1 was the strongest predictor of mortality, independent of CHF severity

Table 6-3 Continued

Study participants						
Author (year)	N	Age (years)	Important inclusions	Exposure	Outcome	Key findings
Deswal et al (2001) [116]	1200	Mean: between 61.6 – 66.1	Advanced HF patients (VEST trial)	Circulating cytokines TNF, IL-6, sTNFR1 & 2, sIL-6 R	Mortality	Increased levels of TNF, IL-6, sTNFR1 & 2 were associated with increased mortality
hs-CRP – high-sensitivity C-reactive protein – is an acute phase reactant that is detectable during systemic inflammation. Hs-CRP is measured in serum and is helpful in assessing cardiovascular disease risk. Reference ranges: Low risk: < 1.0 mg/L; Average risk: 1.0 – 3.0 mg/L; High risk: > 3.0 mg/L; Acute inflammation: > 10.0 mg/L[104, 111]						
Howren et al (2009)[76]	51 studies		Meta-analysis	Depressive symptoms	CRP	Circulating peripheral CRP was significantly associated with diagnosis of major depression
Vaccarino et al (2007)[13]	559	Mean: between 53.9 – 59.2	Women w/ suspected coronary ischemia	Depression: (BDI ≥ 10 & diagnosis of depression) Possible depression: (BDI ≥ 10 OR diagnosis of depression) No depression	CVD events (hospital stays for nonfatal MI, stroke, congestive heart failure, and CVD-related death) Possible mediators: CRP & IL-6	Depression associated with70% higher CRP (p = 0.0008) Possible depression associated with 30% higher CRP (p = 0.02) Depression was a significant predictor of CVD (HR 2.58, p = 0.0009) Possible depression was not a significant predictor of CVD (HR 1.12, p = 0.68) Addition of CRP decreased estimate for depression by 13% Inflammatory biomarkers explain only a small proportion of the association between depression and CVD incidence
Neuhaus et al (2010)[95]	5880 & 3518	45 – 77 & 33 – 44	SMART study / MESA & SMART study / CARDIA	HIV	hsCRP	hsCRP levels were 50% higher (p < .001) among HIV-infected participants compared with levels in MESA study participants hsCRP levels were 55% (p < .001) higher among HIV-infected participants than among CARDIA participants

Table 6-3 Continued

Study participants						
Author (year)	N	Age (years)	Important inclusions	Exposure	Outcome	Key findings
Duprez et al (2012)[113]	5098	Mean: between 49.8 – 56.3	HIV patients enrolled in the SMART study	Hs-CRP	CVD (CVD death, non-fatal MI, non-fatal stroke, congestive HF, coronary revascularization, CAD requiring drug treatment, and peripheral artery disease)	Adjusted HR for CVD Q4 vs Q1: 2.10 (1.40, 3.16)
D-dimer is a marker of coagulation. In a normal state, D-dimer is undetectable. It is elevated in peripheral blood as a result of blood formation and fibrinolysis (blood clot degradation). D-dimer is measured in plasma collected in sodium citrate. The reference range is ≤ 0.5 mcg/mL Fibrinogen Equivalent Units [104, 111]						
Von Kanel et al (2009)[77]	38	Mean: 50	Healthy & Non-smoking German school teachers	Depression (7 item depression subscale of the Hospital Anxiety and Depression Scale)	d-dimer	Depressive symptoms were associated with stress-induced changes in D-dimer levels over time (p = .011) With depressive symptoms, there was an attenuated immediate d-dimer stress response and delayed recovery of d-dimer levels post-stress (prolonged hypercoagulability)
Neuhaus et al (2010)[95]	5880	45 – 77	SMART study / MESA	HIV	d-dimer	d-dimer levels were 94% higher (p < .001) among HIV-infected participants compared with levels in MESA study participants
Armah et al (2012)[80]	2368	Mean: between 51.8 – 53.5	People in the Veterans Aging Cohort Study (VACS)	HIV	D-dimer (>75th percentile)	HIV+ veterans with HIV-RNA ≥ 500 copies/mL had a significantly higher prevalence of elevated d-dimer; OR = 1.97; 95% CI, 1.44 – 2.71) HIV+ veterans with CD4 count <200 cells/µL had a significantly higher prevalence of elevated d-dimer; OR = 1.68; 95% CI, 1.22 – 2.32)
Duprez et al (2012)[113]	5098	Mean: between 49.8 – 56.3	HIV patients enrolled in the SMART study	D-dimer	CVD (CVD death, non-fatal MI, non-fatal stroke, congestive HF, coronary revascularization, CAD requiring drug treatment, and peripheral artery disease)	Adjusted HR for CVD Q4 vs Q1: 2.14 (1.38, 3.33)

Table 6-3 Continued

Study participants						
Author (year)	N	Age (years)	Important inclusions	Exposure	Outcome	Key findings
Neuhaus et al (2010)[95]	5880	45 – 77	SMART study / MESA	HIV	Cystatin C	Cystatin C levels were 27% higher ($p < .001$) among HIV-infected participants compared with levels in MESA study participants
sCD14 is a marker of monocyte activation. It is a biomarker that can be used to monitor monocyte resonse to lipopolysaccharide (LPS), intestinal permeability, and microbial translocation [104, 111]						
Lisi et al (2013)[78]	20	Mean: Between 39.3 – 48.4	Drug free depressed patients	MDD (DSM-IV-TR criteria)	Pro-inflammatory activation of monocytes	Monocytes released the same amounts of prostaglandin E2 (PGE2) Monocytes from depressed patients were dramatically less reactive to lipopolysaccharide
Musil et al (2011)[86]	52	Mean: Between 40.0 – 44.8		Major depression (DSM-IV diagnostic criteria)	sCD14	The levels of sCD14 did not differ between the depressed patients and the healthy controls at any time
Armah et al (2012)[80]	2368	Mean: between 51.8 – 53.5	People in the Veterans Aging Cohort Study (VACS)	HIV	sCD14 (>75th percentile)	HIV+ veterans with CD4 count <200 cells/µL had a significantly higher prevalence of elevated sCD14; OR = 2.60; 95% CI, 1.64 – 4.14)
Sandler et al (2011)[117]	825	Median: between 45 - 50	SMART study participants with HIV & healthy controls	sCD14	Mortality	Subjects with the highest quartile of sCD14 levels had a 6-fold higher risk of death than did those in the lowest quartile

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