ALCOHOL CONSUMPTION AMONG PERSONS LIVING WITH HIV: PATTERNS AND DETERMINANTS OF USE AND IMPACT ON SUBCLINICAL CARDIOVASCULAR DISEASE

By

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To my husband and parents for all of your love and support.

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AIC	Akaike information criteria
AIDS	Acquired immunodeficiency syndrome
AOR	Adjusted odds ratio
ART	Antiretroviral therapy
AUDIT-C	Alcohol Use Disorders Identification Test
BIC	Bayesian information criterion
BMI	Body Mass Index
CACS	Coronary Artery Calcium Score
CCA	Common carotid artery
CCA-IMT μm	Common carotid artery intima medial thickness micrometer
CD4+	Cluster of differentiation 4
CES-D	Center for Epidemiological Studies – Depression
CI	Confidence interval
cIMT	Carotid intima medial thickness
CVD	Cardiovascular disease
ELISA	Enzyme-linked immunosorbent assay
GBTM	Group-based trajectory model
GEE	Generalized estimating equations
HAART	Highly Active Antiretroviral Therapy
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus

ICA	Internal carotid artery
ICC	Internal carotid circulation
IQR	Interquartile range
IRB	Institutional review board
MACS	Multicenter AIDS Cohort Study
MI	Myocardial Infarction
MSM	Men who have sex with men
NHLBI	National Heart, Lung, and Blood Institute
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIH	National Institutes of Health
OR	Odds ratio
PLWH	Persons living with HIV
PP	Propensity probability
HIV RNA	Human immunodeficiency virus Ribonucleic acid
SD	Standard Deviation
WIHS	Women's Interagency HIV Study

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ALCOHOL CONSUMPTION AMONG PERSONS LIVING WITH HIV: PATTERNS AND DETERMINANTS OF USE AND IMPACT ON SUBCLINICAL CARDIOVASCULAR DISEASE

By

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Major: Epidemiology

Cardiovascular disease (CVD) is the most prevalent non-HIV related cause of death among persons living with HIV (PLWH) who are adherent to antiretroviral treatment. After adjusting for CVD-related risk factors, PLWH have a higher rate (11.13/1,000 vs. 6.98/1,000 person-years) and earlier onset for CVD, up to two times the odds for acute myocardial infarction, heart failure, and coronary heart disease, and over five times the risk for stroke, compared to uninfected populations. The higher adjusted risk among PLWH suggests that there are important indicators outside of the traditional CVD risk factor framework, such as alcohol consumption.

Alcohol use is common among PLWH and is reported among 39-81%. Prevalence of hazardous drinking has been reported in as much as 25-45% of PLWH, with alcohol dependence ranging from 5.5-10%. While there is an established J-curve relationship between alcohol consumption and cardiovascular health in the general population, little is known about how long-term drinking behavior effects subclinical cardiovascular disease, also known as atherosclerosis, among PLWH.

Using data from the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study, we characterized patterns of alcohol consumption among PLWH from 2004-2013 by gender and assessed the association between time-stable and –varying clinical factors of long-term heavy and moderate alcohol consumption. We described the association between 10-year patterns of alcohol use and the prevalence and incidence of subclinical atherosclerosis, measured by B-mode carotid artery ultrasound imaging. Last, we assessed the longitudinal association between past (10-year) and current (6-month) patterns of alcohol use and non-plaque carotid intima-media thickness progression.

This study addressed an important gap in the literature regarding the possible J-curve association between alcohol consumption and cardiovascular health, among PLWH, that has been found in the general population. The results of this study will help inform identification of CVD risk among PLWH, and has the potential to highlight the importance of tailored interventions that can better address alcohol use issues.

CHAPTER 1
SCOPE OF THE PROBLEM, LITERATURE REVIEW, AND DISSERTATION AIMS

Introduction

With the introduction of antiretroviral therapies (ART), the life expectancy of persons living with HIV (PLWH) has been substantially prolonged (Wandeler et al., 2016). Thus, prevention and management of age-related chronic illnesses are important targets for HIV-specialists and researchers. Cardiovascular disease (CVD) is immerging as one of the most common comorbidities and causes of death in PLWH (Smith et al., 2014). Further, CVD is the most prevalent non-HIV related cause of death among those who are adherent to ART (Rodger et al., 2013). After adjusting for CVD related risk factors, those with HIV infection have a higher rate (11.13/1,000 vs. 6.98/1,000 person-years) and earlier onset for CVD (Triant et al., 2007), up to two times the odds for acute myocardial infarction (MI; Freiberg et al., 2013; Durand et al., 2011; Triant et al., 2007), heart failure (Butt et al., 2011), and coronary heart disease (Freiberg et al., 2011), and over five times the risk for stroke (Walker et al., 2013; Durand et al., 2012), compared to uninfected populations. Further, PLWH with normal blood pressure had 1.28 times the odds for an acute MI, compared to uninfected controls (Armah et al., 2014). The higher adjusted risk among PLWH suggests that there are indicators outside of the traditional risk factor framework that are important contributors to cardiovascular health, such as alcohol consumption.

Alcohol Consumption Definitions

Alcohol consumption has traditionally been described in terms of level. Moderate alcohol consumption refers to having up to 1 standard drink (12-ounces of beer; 8-ounces of malt liquor; 5-ounces of wine; 1.5-ounces of 80-proof distilled spirits or liquor) per day (0 to 7 standard drinks per week) for women and up to 2 standard drinks per day (0 to 14 drinks per week) from men (Center for Disease Control and Prevention [CDC], 2016). Heavy drinking is considered

consumption > 7 drinks per week for women and > 14 drinks per week for men (CDC, 2016; Reid et al., 1999). Hazardous drinking is considered ≥14 drinks per week for women and ≥ 21 drinks per week for men and is a level that has been associated with increased risk for adverse health events (Reid, 2016). Binge drinking refers to consumption of ≥ 4 drinks for women and ≥ 5 drinks for men in a 2-hour period (CDC, 2016). An alcohol use disorder (AUD) is problematic drinking that meets 2 of the 11 criteria of the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DMS-5) in a 12-month period (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2016). An AUD is classified as mild (2-3 symptoms), moderate (4-5 symptoms), or severe (6 or more symptoms), depending on the number of criteria met. The DMS-5 criteria include symptoms characteristic of alcohol dependence or alcohol abuse (NIAAA, 2016).

Alcohol Consumption among Persons Living with HIV

Alcohol use is common among PLWH and is reported among 39-81% (Bilal et al., 2016; Monroe et al., 2016; Wandeler et al., 2016; Sullivan et al., 2011; Conen et al., 2009). Prevalence of hazardous drinking has been reported in as much as 25-45% (Deiss et al., 2016; Monroe et al., 2016; Kader et al., 2014) of PLWH, with alcohol dependence ranging from 5.5-10% (Jolley et al., 2016; Malbergier et al., 2015; Surah et al., 2013; Sullivan et al., 2011). Alcohol consumption, in general, is negatively associated with completing the steps of the HIV care continuum (Vagenas et al., 2015) and hazardous alcohol use is associated with poor retention in HIV care and lower visit adherence, compared to those that do not drink (Monroe et al., 2016). Likewise, hazardous alcohol consumption is associated with decreased ART adherence (Pellowski et al., 2016; Malbergier et al., 2015; Kalichman, et al., 2014; Tran et al., 2014), lower CD4+ T-cell count (Kahler et al., 2015; Malbergier et al., 2015), and increased viral load (Deiss et al., 2016).

Aside from the relationship between alcohol consumption and ART adherence, alcohol abuse has been linked specifically to HIV progression through alteration of viral infectivity, inflammatory biomarkers, immune response, and tissue injury (Monnig et al., 2016; Molina et al., 2014). Hazardous drinking in this population is also associated with engagement in risky health behavior, such as cigarette smoking (Braithwaite et al., 2016; Pacek et al., 2014) and substance use (Parsons et al., 2014), which can lead to other chronic illnesses. Some studies have found that PLWH who use alcohol have increased chronic comorbidity (Bilal et al., 2016; Jolley et al., 2016; Kelso et al., 2015), while other studies have found no such association (Kelly et al., 2016; Tsui et al., 2016; Wandeler et al., 2016; Fuster et al., 2013). Because many of the aforementioned studies are cross-sectional, it is unclear whether moderate and hazardous drinking leads to chronic illness or if alcohol use is a coping response to such illness. Further, emerging evidence suggests that PLWH may be more affected by the harmful sequela of alcohol use when compared to similar or lower levels of use among uninfected groups (Justice et al., 2016; McGinnis et al., 2016; Rentsch et al., 2016).

Alcohol Consumption and Cardiovascular Risk Factors

The mechanism by which alcohol consumption is thought to effect cardiovascular health among PLWH is complex, not well understood, and of great practical importance given the widespread global consumption of alcohol (Freiberg and So-Armah, 2016). Biological and behavioral mechanisms are thought to explain the higher burden of CVD among PLWH, shown in our conceptual model (Figure 1-1).

Heavy alcohol consumption and CVD are affected by demographic and psychosocial factors, including age, education, race/ethnicity, and socioeconomic status (Conen et al., 2009; Galvan et al., 2002). Alcohol use is also associated with other risky health behaviors, such as

tobacco use (Cook et al., 2013). injection drug use (Chitsaz et al., 2013; Conen et al., 2009) and depressive symptoms (Sullivan et al., 2011).

Alcohol use is significantly associated with traditional CVD risk factors, including dyslipidemia (high triglyceride and low-density lipoprotein cholesterol levels [LDL]; Hejazi, et al., 2013; Míguez-Burbano et al., 2009; Hadigan et al., 2001), and insulin resistance (type II diabetes; Justice et al., 2006; Hadigan et al., 2001). Specifically, different levels of alcohol consumption tend to have a differential effect on important cardiovascular risk factors and biomarkers. For example, compared to non-drinkers, moderate alcohol consumption (1 drink per day in women or up to 2 drinks per day in men) is associated with a 10% increase in HDL cholesterol (Brinton, 2012). Heavy alcohol consumption is associated with an even greater increase in HDL, but is paradoxically associated with increases in triglyceride, LDL, and total cholesterol levels (Khanh et al., 2016; Brinton, 2012). Further, compared to never drinkers, those who consumed 2-7 drinks per week were less likely to have increases in damaging cardiac biomarkers (i.e., high sensitivity cardiac troponin T and N-terminal pro B-type natriuretic peptide); however, those who consumed 15 or more drinks per week were more likely to have incident increases in these same biomarkers (Lazo et al., 2016).

Alcohol consumption may increase the development of CVD through HIV related factors. HIV-infection alone increases systemic inflammation (Bahrami et al., 2016; Shrestha et al., 2014) and immune activation (Maniar et al., 2013; Neuhaus et al., 2010; Hsue et al., 2009; Strategies for Management of Antiretroviral Therapy Study Group et al., 2006), which are pathophysiologic responses that contribute to the risk for CVD (Bahrami et al., 2016, Hsu et al., 2016, Hansson, 2005). Use of ART results in reduced inflammation through HIV RNA viral load suppression; however, alcohol consumption is associated with decreased ART adherence, thus

resulting in higher HIV RNA viral load and lower CD4+ T-cell count (Hendershot et al., 2009). Chronic inflammation and immune activation can lead to the breakdown of the endothelial walls of the gastrointestinal tract, a process that leads to microbial translocation which triggers further immune and pro-inflammatory responses (D'Abramo et al., 2014; Klatt et al., 2013; Maniar et al., 2013). Previously mentioned, low level consumption of alcohol may have favorable lipid or antithrombotic effects. Paradoxically, low levels of alcohol use have also been shown to increase systemic inflammation, as well as risk for microbial translocation (Brenchley and Douek, 2012). Through this pro-inflammatory process, the endothelial wall loses structural integrity, allowing microbial material and bacteria to enter the bloodstream and cause buildup within arteries, leading to cardiovascular complications (Klatt et al., 2013; Brenchley et al., 2012; Freiberg and Kraemer, 2010). Additionally, heavy alcohol consumption is associated with frequent switching off treatment, HIV duration, and Hepatitis C co-infection (Conen et al., 2009).

Alcohol Consumption and Cardiovascular Disease

Moderate alcohol consumption may be protective against CVD, with over moderate use being a risk factor in the general population (Mukamal et al., 2003a; Reynolds et al., 2003; Corrao et al., 2000; Sacco, et al., 1999; McElduff and Dodson, 1997). Several studies have indicated significant crude positive associations between any alcohol use (Twagirumukiza et al., 2007), heavy alcohol use (Longo-Mbenza et al., 2011), history of alcohol abuse or dependence (Durand et al., 2012) and clinical CVD among PLWH. Additionally, heavy alcohol use (Freiberg et al., 2010; Corral et al., 2009) and abuse/dependence (Freiberg et al., 2010; Justice et al., 2008) are cross-sectionally associated with increased odds for CVD, after adjusting for CVD and HIV related risk factors. Some studies among PLWH found moderate alcohol consumption to be associated with lower adjusted hazard ratio for CVD, compared to alcohol abstainers (Wandeler et al., 2016; Carrieri et al., 2012). The current state of the literature is limited to mostly cross-

sectional methods and/or investigation of vague measures of alcohol use (e.g., any alcohol use, alcohol abuse/dependence history) to characterize risk among majority male HIV infected participants (Kelso et al., 2015). Further, most studies utilize only the medical record to classify diagnosis of clinical CVD, and do not assess early stages of disease development, such as atherosclerosis.

Alcohol Consumption and Atherosclerosis

Subclinical CVD, also known as atherosclerosis, is characterized by arterial plaques that may narrow the lumen, decrease blood flow and consequently predispose individuals to acute thrombotic events (National Institutes of Health [NIH], 2011). This process is precursory to CVD, and can lead to serious events, such as MI and stroke (NIH, 2014). Because atherosclerosis is asymptomatic and not typically assessed in clinical settings, it is difficult to know the prevalence and incidence of this subclinical disease. Most studies of atherosclerosis focus on prevalence and incidence of atherosclerosis in certain clinical populations. One recent study of men and women aged 40-54 years found the prevalence of atherosclerosis to be 63% (71% in men, 48% in women; Fernandez-Friera et al., 2015). The Multi-Ethnic Study of Atherosclerosis detected prevalent and incident atherosclerosis, measured by a positive coronary calcium score (CACS), in 48% and 20%, respectively (Pandey, 2014) Atherosclerosis is an independent risk factor for clinical cardiovascular events. One study found that those with atherosclerosis at baseline had twice the risk for incident CVD events, compared to those without atherosclerosis (25.8% vs. 12.2%; Robinson et al., 2009). Further, plaque formation from baseline to follow-up was significantly associated with incident CVD events (Hazard Ratio 1.22, CI 1.05-1.42, $p<.01$), with new plaque formation adding significant predictive value (+8%) in Receiver Operating Characteristic Curve Analysis (Benedetto et al., 2008). If atherosclerosis is detected and depending on the severity of disease and present risk factors, treatment could

include lifestyle modification (i.e., heart-healthy eating, weight management, stress management, physical activity, and smoking cessation), medication (to lower cholesterol and/or blood pressure or to regulate blood sugar), or medical procedures for more severe atherosclerosis (i.e., coronary angioplasty, coronary artery bypass grafting, carotid endarterectomy; National Heart, Lung, and Blood Institute [NHLBI], 2016).

While many clinicians identify those at risk for CVD by assessing the presence of traditional CVD risk factors alone (including age, sex, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, and use of blood pressure medications), assessing the presence of subclinical CVD is a more sensitive representation of those who may be at risk for CVD (George and Movahed, 2008). Non-invasive tests used to identify subclinical CVD have been shown to detect those at high risk for clinical CVD who would have otherwise been considered lower risk according to the traditional risk factors (Church et al., 2007).

Non-invasive assessment of subclinical CVD is most often by use of high-resolution B-mode carotid artery ultrasound or by computed tomography. The carotid artery ultrasound detects carotid intima-media thickness (cIMT; the thickness of the inner and middle layers of the carotid artery), carotid stiffness, and presence of arterial plaque/lesions (Stein et al., 2008). Computed tomography is used to calculate a CACS and detects presence of calcification of coronary arteries (Lester et al., 2009). While both tests characterize subclinical CVD, these tests measure different aspects of asymptomatic disorder, and thus are not strongly correlated (Oei, et al., 2002; Davis et al., 1999). Furthermore, research has suggested that carotid artery ultrasound has higher sensitivity, and can detect subclinical CVD among those with a low CACS (Lester et al., 2009; Davis et al., 1999). Further, use of cIMT and plaque information measured by carotid artery ultrasound has been shown to significantly improve coronary heart disease risk prediction

over traditional risk factors (by 3.8%, Polak et al., 2015; by 23%, Nambi et al., 2010; by 20% in men and 1% in women, Nambi et al., 2012). Further, cIMT was significantly associated with incident CVD events after adjusting for traditional CVD risk factors (Hazard Ratio 1.63, CI 1.12-2.37; Polak and O'Leary, 2015).

There is little research investigating the association between alcohol consumption and atherosclerosis. In the general population, moderate alcohol use has been cross-sectionally associated with 55% lower risk for carotid artery plaque (95% CI 0.29-0.68, $p<.001$; Kohsaka et al., 2011) and statistically significantly lower arterial stiffness (Hougaku et al., 2005), compared to abstinence. Heavy alcohol use, however, has been associated with a significant increase in cIMT (Zyriax et al., 2010) and stiffness (Hougaku et al., 2005), consistent with a J-curved association found in the literature (Xie et al., 2012; Mukamal et al., 2003). Similarly, a longitudinal study of 20-year drinking patterns found that consistent heavy use was associated with a significant increase in cIMT, compared to consistent moderate use (Britton et al., 2016). Other studies have found no significant association between alcohol consumption and cIMT or presence of carotid plaques (Kim et al., 2014; Bauer et al., 2013; Zureik et al., 2004). Some studies have found significant associations between alcohol consumption and subclinical disease in men, but not in women (Zyriax et al., 2010; Lee et al., 2009; Schminke et al., 2005).

Gender and Atherosclerosis

With acute cardiac syndromes (myocardial infarction, stroke, angina pectoris) on the rise in women (Izadnegahdar et al., 2014; Sozzi et al., 2007), research on sex (biological) and gender (social) disparities in CVD has grown in recent years. Even with growing interest in such disparities, gender differences have not been adequately investigated and significant gaps in the literature exist regarding possible differences in biological and behavioral mechanisms of disease. With regard to sex differences, the onset of CVD generally occurs 10-years later in

premenopausal women than in men, with MI occurring 20 years later (Mathur et al., 2015). While men have traditionally been at higher risk for CVD, after menopause women have 10 times the risk for CVD, while men have a 4.6 times increase compared to the same age groups (Duvall, 2003). In fact, a contributing role may be the observed low LDL cholesterol and high HDL cholesterol up until menopause (Mathur et al., 2015). Other studies have found that traditional CVD risk factors may be more biologically detrimental in women, compared to men. For instance, in large, longitudinal epidemiologic studies smoking behavior (Njolstad et al., 1996) and diabetes (Stokes, et al., 1987) have to shown to be greater risk factors for CVD in women than men. Another biological sex difference is size of arteries. Women tend to have smaller carotid arteries (Schulz and Rothwell, 2001; Krejza et al., 2006), less plaque in these arteries, but more significant stenosis (Iemolo, et al., 2004), compared to men. Further, atherosclerosis in women is more likely to present as microvascular coronary disease, rather than plaque development and narrowing of the large coronary arteries (Vaccarino and Bremner, 2016). Therefore, it is possible that moderate and heavy drinking are associated with early progression of CVD, but in the small arteries and vessels of the coronary arteries.

Gender differences have also been described in more recent literature. For example, neighborhood socioeconomic status and high professional status was found to be inversely associated with cIMT in women, but not in men (Grimaud et al., 2013). In the longitudinal Multi-Ethnic Study of Atherosclerosis, educational status was also found to be linked to significantly slower stiffening of the carotid artery in women, but not in men (Stern et al., 2015). Psychological factors, such as chronic stress, trauma history, and depressive symptoms have also been associated with poor cardiovascular outcomes, but exponentially more so in women (Xu et al., 2015; Vaccarino et al., 2014; Rich-Edwards et al., 2012; Korkeila et al., 2010). For example,

in a longitudinal study of nearly 8,000 adult men and women in the United States, women with depression or a history of attempted suicide had 3.20 (CI 1.12-9.17) and 14.57 (CI 2.65-80.10) times higher risk for CVD and ischemic heart disease, respectively, while the corresponding risk for men was 2.37 (CI 0.85-6.58) for CVD and 3.52 (CI 1.05-11.76) for ischemic heart disease (Shah et al., 2011). Because of these sex and gender differences in CVD and risk, it is important to consider the association between alcohol consumption and atherosclerosis separately for men and women.

Limitations of the Current Literature

To our knowledge, only three studies exist for which the main objective was to assess the relationship between alcohol consumption and CVD among PLWH (Wandeler et al., 2016; Carrieri et al., 2012; Freiberg et al., 2010) and only one study assessed the cross-sectional association between alcohol and atherosclerosis (Hanna, et al., 2015). Given the high mortality and morbidity associated with clinical CVD, identifying those with subclinical atherosclerosis and modifiable risk factors is a high priority for primary and secondary prevention strategies.

Dissertation Significance

This dissertation responds to the National HIV/AIDS Strategy for the United States to increase access to care and improve health outcomes for PLWH (The White House Office of National AIDS Policy, 2010), as well as the NIH objectives to advance discovery of therapeutic strategies to prevent HIV comorbidities across the lifespan and to determine the link between HIV and associated comorbidities (NIH Office of AIDS Research, 2014). The research also aims to address the NIAAA objective to understand how alcohol use influences mortality among PLWH (NIAAA, 2014) and research focus of the NHLBI on the contribution of HIV related risk factors on the development of CVD (NHLBI, 2014). The current dissertation seeks to advance scientific knowledge of risk factors for subclinical CVD that extend beyond cross-sectional

measurement of traditional risk factors among PLWH. We aimed to assess the J-curve association between alcohol consumption and cardiovascular health among PLWH, and to provide evidence that addresses the specific relationships between moderate and heavy use on subclinical atherosclerosis. We had the unique opportunity to carry out our study aims using the data from 2,149 participants from the Cardiovascular Substudies of the Women's Interagency HIV Study (WIHS) and the Multicentered AIDS Cohort Study (MACS). We used this longitudinal data to describe 10-year alcohol consumption patterns by using self-reported quantity and frequency of use. We used state-on-the-art methodology to identify hypothesized patterns of alcohol consumption through group-based trajectory analysis. Further, we have a sensitive measure of subclinical CVD, through use of B-mode carotid artery ultrasound to detect the presence of carotid artery plaques and non-plaque cIMT progression.

Summary

In summary, few studies have focused on the impact of alcohol use on cardiovascular health among PLWH. Among these studies, none have assessed the impact of long-term alcohol consumption patterns and how these patterns effect the subclinical development of CVD. The results of this study will have implications for more effective identification of PLWH with high CVD risk outside of the traditional CVD risk framework, affecting clinical practice. This research also has implications for better recommendations for clinical prevention services and has the potential to highlight the importance of tailored interventions that can better address alcohol use issues that are specific to PLWH.

Dissertation Aims

AIM 1: To determine 10-year alcohol consumption patterns among HIV infected men and women and to identify factors associated with alcohol consumption patterns. Because of limitations of the current literature, a gap exists regarding whether alcohol use

behaviors change over time among PLWH. Further, it is unclear if there are significant clinical factors associated with long-term moderate and heavy alcohol consumption by gender. Associated factors of alcohol consumption patterns would provide clinicians with the means to identify those with the greatest need for early intervention and alcohol abuse treatment. The goals of Aim 1 were to 1) describe patterns of alcohol consumption among PLWH from 2004-2013 by gender and 2) assess the association between time-stable and –varying clinical factors and long-term heavy and moderate alcohol consumption. By utilizing reported number of drinks per week, we hypothesized that distinct patterns would emerge that are descriptive of stable (i.e., consistent abstinent, consistent moderate, and consistent heavy) and changing alcohol use behavior (i.e., abstinent to moderate or heavy drinking; heavy to moderate or abstinence) over time. We also hypothesized that clinical factors would be identified, specifically by gender, as important predictors of long-term moderate and heavy alcohol consumption. Specifically, we hypothesized that those with poor clinical profiles would be more likely to be heavy or moderate drinkers, compared to those who are abstinent or low drinkers. While clinical associations of longitudinal alcohol consumption were the main focus of this analysis, the biopsychosocial theoretical framework (Engel GL, 1977) was used to conceptualize other non-clinical factors needed for analytical adjustment.

AIM 2: To determine the effect of 10-year alcohol consumption patterns on prevalent and incident subclinical atherosclerosis among PLWH. The objective of Aim 2 was to assess the association between 10-year patterns of alcohol use and the prevalence and incidence of subclinical atherosclerosis, measured by B-mode carotid artery ultrasound imaging. Specifically, we aimed to 1) test the association between long-term moderate and heavy alcohol use and subclinical atherosclerosis among PLWH, and 2) to explore whether the relationships

appeared to differ by gender and between prevalent and incident disease. We hypothesized that long-term moderate and heavy alcohol use would be significantly associated with increased risk for prevalent and incident subclinical atherosclerosis.

AIM 3: To determine the effect of past (10-year) and current (6-month) alcohol consumption patterns on the early development of subclinical atherosclerosis among PLWH. Specifically, we aimed to 1) assess the relationship between past (10-year) and current (6-month) alcohol consumption patterns and non-plaque cIMT progression among PLWH, and 2) explore whether the relationships appeared to differ by gender. We hypothesized that past alcohol consumption patterns would be more significantly associated with increases in cIMT versus current alcohol consumption. Specifically, we expected that 10-year patterns of moderate consumption would be associated with a protective effect and heavy consumption would be associated with a harmful effect on cIMT.

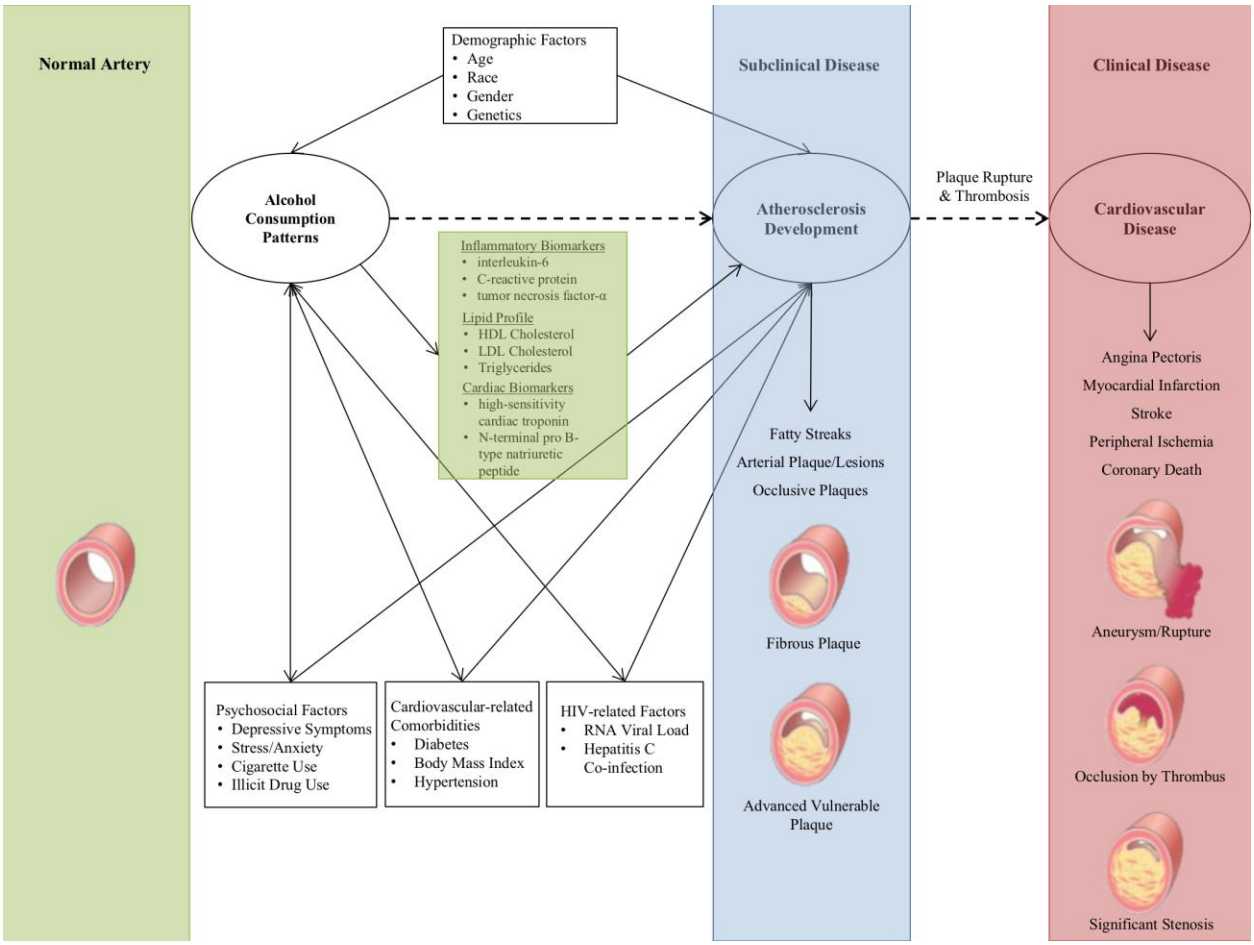

Figure 1-1. Factors associated with the the relationship between alcohol consumption on atherosclerosis. Images taken from Kumar V et al. (2007).

CHAPTER 2
GENERAL MATERIALS AND METHODS

Study Setting, Selection, and Inclusion Criteria

The proposed study is a secondary analysis of the Cardiovascular Substudies of the multicenter longitudinal cohort studies of WIHS (Bronx, Brooklyn, Chicago, District of Columbia, Los Angeles, and San Francisco) and MACS (Baltimore/District of Columbia, Chicago, Los Angeles, and Pittsburgh). We used data that had been collected from 1994-2014 to test the specific aims of the current dissertation. The MACS (Dudley et al., 1995; Detels et al., 1992, Kaslow et al., 1987) and WIHS (Bacon et al., 2005; Barkan et al., 1998) are well-established, national multicenter cohorts of men who have sex with men (MSM) and of women, respectively, living with or at risk for HIV-infection. The MACS recruited MSM across three waves, in 1984-1985 (n=4954), 1987-1991 (n=668), and 2001-2003 (n=1350). Women were recruited in WIHS across two waves, in 1994-1995 (n=2625) and 2001-2002 (n=1141). The data were collected through structured interviews, and standardized physical, psychological, and laboratory assessments. HIV status was assessed by enzyme-linked immunosorbent assay (ELISA) with Western blot for confirmation at baseline for HIV+ participants, and semi-annually for HIV- participants. HIV sero-conversion was confirmed by testing HIV- participants at each semi-annual visit. Written informed consent was obtained prior to each semi-annual assessment for both cohorts. The questionnaires are available online for MACS at http://aidscohortstudy.org and for WIHS at https://statepi.jhsph.edu/wihs/wordpress/.

The WIHS Cardiovascular Substudy consists of 1,321 HIV infected women aged 25 to 60 years, with no history of heart surgery or coronary angioplasty/stent placement before HIV infection. Mean age ranged from 40.4-42.2 years (Parrinello et al., 2012), 60.4% of the sample is African American, 22.6% White, and 17% other. About 29% of the sample was of Hispanic

ethnicity. The mean CD4+ T-cell count was between 377-462, and mean HIV RNA $\log_{10}$ copies/mL was between 2.5-3.7 (Parrinello et al., 2012). The MACS Cardiovascular Substudy consists of 828 HIV infected MSM over 40 years of age, under 300lbs, with no history of heart surgery or coronary angioplasty/stent placement before HIV infection (Miller et al., 2014). Mean age ranged from 49.2-56.7 years, 61.4% of the sample was White, 32.2% African American, and 6.4% other. Regardless of race, 10.9% of the sample was of Hispanic ethnicity. The mean CD4+ T-cell count was between 597-628, and mean HIV RNA $\log_{10}$ copies/mL was between 2.4-3.2 (Miller et al., 2014). At the first subclinical CVD assessment, 10.3% of HIV infected women (Crystal et al., 2011) and 23.5% of men were identified as cases with subclinical CVD (Monroe et al., 2012). Also at first assessment, drinking ranged from abstinence (women=54%, men=20%), 1-2 drinks per week (women=35%, men= 56%), and over 2 drinks per week (women=11%, men=24%; Kaplan et al., 2008).

In addition to the standard data collection for the MACS and WIHS, participants in the cardiovascular sub-studies underwent high-resolution B-mode carotid artery ultrasounds of 6 locations in the right carotid artery (the near and fall walls of the common carotid artery [CCA], carotid bifurcation, and internal carotid artery [ICA]; Hodis et al., 2001), using a standardized protocol across study sites (Kaplan et al., 2008). Quality control and reliability of the carotid artery ultrasound measurement was performed among a subset of WIHS and MACS participants and was found to have high intraclass correlations (ICC) in both WIHS (variation coefficient = 1.8%; ICC = 0.98) and MACS (variation coefficient = 1.0%; ICC=0.99; Kaplan et al., 2008).

Measures

Independent Predictor

Alcohol consumption. The WIHS and MACS collected data on alcohol consumption semiannually. Participants were asked how many days on average they consumed alcohol

(frequency) and how many standard units of alcohol were consumed on a drinking day (quantity). The average number of alcoholic beverages consumed per week was calculated by multiplying the frequency by the quantity of use at each semiannual visit.

Dependent Outcome

Atherosclerosis. Atherosclerosis was measured using B-mode carotid artery ultrasound between 2004-2013. Presence of an arterial lesion or plaque, which was a focal carotid intima-media thickness over 1.5mm (Stein et al., 2008), was measured up to 2 times from 2004-2013. Carotid intima media thickness at the far right common carotid artery (CCA-IMT) was measured up to 4 times in WIHS and up to 3 times in MACS from 2004-2013. The CCA-IMT was assessed using the B-mode carotid artery ultrasounds by automated computerized edge detection of the images.

Development of atherosclerosis was defined in three ways. First, lesions or plaques present at baseline assessment were considered prevalent cases. Second, participants that screened negative for lesions or plaques at the baseline assessment, but were screened positive at the follow-up were considered incident cases. Third, as change in CCA-IMT from the baseline to each subsequent follow-up assessments.

Covariates of Interest

Conceptual model with covariates are shown in Figure 1-1.

Demographics factors. Age was assessed in years, using participants' self-reported date of birth. Race was self-reported and categorized as white, black, and Asian/Pacific Islander or Native American/Alaskan. Annual income was self-reported at each visit and categorized, based on natural cut-offs in the data, as < $10,000, $10,000-$30,000, or ≥ $30,000 a year.

Behavioral factors. Self-reported smoking was assessed in number of packs smoked using standardized categories: less than half a pack per day; at least half a pack but less than one

pack per day; at least one but less than two packs per day; two or more packs per day. Cumulative pack-years were calculated to determine the average pack, multiplied by 0.5 (half a year to reflect the timeframe of the seminannual visits), and summed across the years up to the baseline and follow-up assessments. Self-reported illicit drug use was dichotomous and measured by asking if participants used any of the following: crack or any form of cocaine; uppers (including crystal, methamphetamines, speed, ice); heroin or other opiates. Depressive symptoms were assessed at each semi-annual visit with the Center for Epidemiology Studies Depression Scale (CES-D, Radloff, 1977). Some research has found that utilizing the score of 16 or greater may inflate the rate of depression among PLWH, due to the overlapping somatic symptoms that may be present due to HIV-infection (Kalichman et al., 2000). Therefore, a score of 23 or greater was considered probable depression.

HIV-related factors. Plasma HIV RNA viral load and CD4+ T-cell count was measured using standard laboratory techniques. HIV RNA viral load was categorized as suppressed (< 200 copies/mL) or unsuppressed (≥ 200 copies/mL; AIDSinfo, 2016); CD4+ T-cell count was categorized as high (≥500 cells/mm3), medium (300 – 500 cells/mm3), or low (< 300 cells/mm3). Cumulative ART use was calculated by adding the weighted ART use variable to reflect years of ART use by the end of the 10-year follow-up period. Optimal ART adherence was defined as taking ≥ 95% of prescribed ART doses at each semiannual visit, as this has previously been associated with sustained viral suppression (Low-Beer et al., 2000; Paterson et al., 2000).

Cardiovascular-related factors. Cardiovascular risk factors included body mass index (BMI; underweight <18.5 kg/m^2, normal 18.5-24.9 kg/m^2, overweight >24.9 kg/m^2), hypertension (blood pressure ≥ 140/90 or if the participant had been told by a doctor that they

have hypertension) and diabetes (dichotomized as having been diagnosed with diabetes versus no history of diabetes). The Framingham Risk Score (Wilson et al., 1998) was calculated, using the gender-based algorithms, including the following variables: age, total cholesterol, high density lipoprotein (HDL) cholesterol, systolic blood pressure, and smoking status. Therefore, we did not adjust for these variables outside of this risk score in analyses where the Framingham Risk Score was used. The Framingham Risk Score values range from negative to positive, with negative values indicating low risk and positive values indicating high risk.

Data Analysis

Throughout all aims of the dissertation, Group-based Trajectory Modeling (GBTM) was used to categorize alcohol consumption patterns, and warrants discussion. There are several situations in which GBTM is appropriate and needed. First, GBTM is particularly important when a predictor or outcome is one that often changes overtime. When we have time-dependent data, it is more accurate to characterize that change, as opposed to using one time-point and no assessment of change over time. Second, GBTM also allows us to identify individual variability of a mean population trend. We can better assess the qualitative dimensions of changes that occur over time or with age in a particular behavior, such as alcohol use. Therefore, GBTM allows us to take a more person-based approach to analyze change, and to identify distinct patterns of change that are substantively meaningful, and that do not assume a general mean change pattern of an entire sample. Third, GBTM allows us to identify distinctions between important subgroups of a population of interest, that is more representative of the natural setting, as most populations are heterogeneous in nature. Fourth, GBTM are very helpful when there is more than linear change over time. Because the analysis allows us to identify linear, quadratic, and cubic patterns of a particular behavior, we can more accurate assess how change occurs that

is beyond a simple linear representation. Lastly, a benefit of the GBTM includes the ability to estimate proportion of the sample that are characterized in a specific trajectory or subgroup.

There are limitations to GBTM that should be considered. The GBTM is a semi-parametric and probabilistic model that estimates grouped trajectories of the most similar individual patterns. Therefore, each trajectory group does not fully describe the individual-level patterns contained within them and should not be considered absolute. Further, the validity of GBTM relies heavily on the professional judgment of the investigator. This is specifically regarding the number of trajectories and the type of change (linear, quadratic, etc.) to specify. Therefore, it is of high importance to assess the existing literature on the variable in question to understand the patterns that are already known to exist. This method is also not suitable for variables that change rarely over time, such as chronic illnesses that are quite stable.

IRB review

All MACS and WIHS participants provided written informed consent for overall study and sub-study participation. This specific analysis was approved by MACS and WIHS and the Institutional Review Board at the University of Florida.

CHAPTER 3
ASSOCIATION BETWEEN ALCOHOL CONSUMPTION TRAJECTORIES AND CLINICAL PROFILES AMONG MEN AND WOMEN LIVING WITH HIV

Introduction

Alcohol use is common among persons living with HIV (PLWH) and is reported among 39-81% (Bilal et al., 2016; Conen et al., 2009; Monroe et al., 2016; Wandeler et al., 2016; Sullivan et al., 2011). Prevalence of heavy drinking has been reported in as much as 25-45% (Deiss et al., 2016; Monroe et al., 2016; Kader et al., 2014) of PLWH, with alcohol dependence ranging from 5.5-10% (Jolley et al., 2016; Malbergier et al., 2015; Surah et al., 2013; Sullivan et al., 2011). Alcohol consumption, in general, is negatively associated with completing the steps of the HIV care continuum (Vagenas et al., 2015) and heavy alcohol use is associated with poor retention in HIV care and lower visit adherence, compared to those who do not drink. Likewise, heavy alcohol consumption is associated with decreased antiretroviral (ART) adherence (Pellowski et al., 2016; Malbergier et al., 2015; Kalichman et al., 2014; Tran et al., 2014), lower CD4+ T-cell count (Kahler et al., 2015; Malbergier et al., 2015), and increased viral load (Deiss et al., 2016). Aside from the relationship between alcohol consumption and ART adherence, alcohol abuse has been linked specifically to HIV progression through alteration of viral infectivity, inflammatory biomarkers, immune response, and tissue injury (Monnig et al., 2016; Molina et al., 2014). Heavy drinking in this population is also associated with engagement in risky health behavior, such as cigarette (Braithwaite et al., 2016; Pacek et al., 2014) and substance use (Parsons et al., 2014), which can lead to other chronic illnesses. Some studies have found that PLWH who use alcohol have increased chronic comorbidity (Balal et al., 2016, Jolley et al., 2016; Williams et al., 2016; Kelso et al., 2015), while other studies have found no such association (Kelly et al., 2016; Tsui et al., 2016; Wandeler et al., 2016; Fuster et al., 2013). Others have found a J-curve association between alcohol consumption and risk for chronic

illness. For example, Wandeler et al. (2016) found that, among PLWH, low and moderate drinkers had significantly lower risk for cardiovascular disease events or death, compared to non-drinkers. Because many of the aforementioned studies are cross-sectional, it is unclear whether moderate and heavy drinking leads to chronic illness or if alcohol use is a coping response to such illness. While similar findings have been shown in the general population, emerging evidence suggests that PLWH may be more affected by the harmful sequela of alcohol use when compared to similar or lower levels of use among uninfected groups (Justice et al., 2016; McGinnis et al., 2016; Rentsch et al., 2011).

Longitudinal studies of alcohol use patterns among PLWH have focused primarily on dichotomous measures of hazardous or heavy alcohol use, which limit the variability of alcohol consumption and can result in stagnated patterns over time (Marshall et al., 2015a ; Jacob et al., 2013). These studies have also been limited by relatively short follow-up (6 months – 2 years) (Marshall et al., 2015a; Míguez-Burbano et al., 2014) or have synthesized longitudinal patterns by using lifetime recall of alcohol use phases (Jacob et al., 2013). To our knowledge, there is limited research on levels of alcohol use aside from hazardous/heavy use over long periods of follow-up. Cook et al. (2013) conducted a group-based trajectory model (GBTM) of self-reported number of drinks consumed per week to inform emerging patterns among HIV+ women in the Women's Interagency HIV Study (WIHS) from 1996-2006. This study found five trajectories of drinking, three of which described changing drinking behavior over time. These data, however, describe drinking patterns in the first half of the 20-year cohort study and may not be relevant to drinking behavior in the post-HAART era. Lastly, Marshall et al (2015b) conducted a longitudinal analysis of patterns of the Alcohol Use Disorder Identification Test-Consumption questionnaire (AUDIT-C; Surah et al., 2013) score among HIV+ men who have

sex with men (MSM) from 2002-2010 of the Veteran's Aging Cohort Study. This study found four stable trajectories, perhaps due to the use of the somewhat prescriptive AUDIT-C score, which is used to identify alcohol use disorders (score ranging from 0 to 12) and has lower variability than that of self-reported number of drinks per week, thus limiting the detection of change in drinking. While these two studies were conducted in different populations and examined inconsistent predictors of heavy alcohol use, illicit drug use was distinctly associated with heavy consumption.

Because of limitations of the current literature, a gap exists regarding alcohol use changes over time among PLWH. Further, it is unclear if there are significant clinical factors associated with long-term moderate and heavy alcohol consumption by gender. Associated factors of alcohol consumption patterns would provide clinicians with the means to identify those with the greatest need for early intervention and alcohol abuse treatment. The goals of this analysis are to 1) describe patterns of alcohol consumption among PLWH from 2004-2013 by gender and 2) assess the association between time-stable and –varying clinical factors and long-term heavy and moderate alcohol consumption. By utilizing reported number of drinks per week, we hypothesized that distinct patterns will emerge that are descriptive of stable (i.e., consistent abstinent, consistent moderate, and consistent heavy) and changing alcohol use behavior (i.e., abstinent to moderate or heavy drinking; heavy to moderate or abstinence) over time. We also hypothesized that clinical factors would be identified, specifically by gender, as important predictors of long-term moderate and heavy alcohol consumption. Specifically, we hypothesized that those with poor clinical profiles would be more likely to be heavy or moderate drinkers, compared to those who are abstinent or low drinkers. While clinical associations of longitudinal alcohol consumption were the main focus of this analysis, the biopsychosocial theoretical

framework (Engel, 1977) was used to conceptualize other non-clinical factors needed for analytical adjustment.

Methods

Study Design and Participants

The Multicenter AIDS Cohort Study (MACS) (Dudley et al., 1995; Detels et al., 1992; Kaslow et al., 1987) and Women's Interagency HIV Study (WIHS) (Bacon et al., 2005; Barkan et al., 1998) are well-established, national multicenter cohorts of men who have sex with men (MSM) and of women, respectively, living with or at risk for HIV-infection. Participants from MACS were recruited from the following metropolitan areas: Baltimore, MD; Washington, DC; Chicago, IL; Pittsburgh, PA; Los Angeles, CA. Participants from WIHS were recruited from the following metropolitan areas: Brooklyn and Bronx, NY; Washington, DC; Chicago, IL; Los Angeles and San Francisco, CA. The MACS recruited MSM across three waves, in 1984-1985 (n=4954), 1987-1991 (n=668), and 2001-2003 (n=1350). Women were recruited in WIHS across two waves, in 1994-1995 (n=2625) and 2001-2002 (n=1141). The data from these studies were collected from structured interviews, and standardized physical, psychological, and laboratory assessments. HIV status was assessed by enzyme-linked immunosorbent assay (ELISA) with Western blot for confirmation at baseline for HIV+ participants, and semi-annually for HIV- participants. Sero-conversion was confirmed by testing HIV- participants at each semi-annual visit using the aforementioned tests. Written informed consent was obtained prior to each semi-annual assessment for both cohorts. The questionnaires are available online for MACS at www.statepi.jhsph.edu/macs/forms.html and for WIHS at https://statepiaps.jhsph.edu/wihs/index-forms.htm. The current study utilized data from participants of the cardiovascular sub-studies of the MACS and WIHS, to understand the associations between clinical profiles including cardiovascular disease risk factors (i.e.,

Framingham risk score, BMI, diabetes) and alcohol consumption prior to cardiovascular disease or related events. All MACS and WIHS participants provided written informed consent for overall study participation, and this specific analysis was approved by the Institutional Review Board at the University of Florida.

Data Collection

The cardiovascular sub-study enrolled a subset of HIV+ WIHS participants (n=1,321), aged 25-60 years and the MACS enrolled a subset of HIV+ MSM (n=828), over 40 years of age and under 300 lbs. Participants who seroconverted during the study and those with less than 4 alcohol consumption assessments were excluded (WIHS n=198; MACS n=231). The median person-years of follow-up between 2004-2013 were 6.2 years [interquartile range (IQR): 6.0-7.5 years] for WIHS participants and 8.5 years (IQR: 8.0-10.0 years) for MACS participants.

Main outcome measure

Alcohol consumption was measured via self-report by asking about the average frequency (number of days per week) and quantity (number of drinks per drinking day) of use. The average number of drinks per week was calculated by multiplying the frequency by the quantity; consumption was categorized as abstinence to low (<1 drink per week), moderate (1-7[14] drinks per week for women [men]), or heavy use (> 7[14] drinks per week for women [men]).

Independent variables

Clinical and biological. Age was assessed in years, using participants' self-reported date of birth. Use of ART was reported at each visit and weighted by the reported adherence of ART (Shoptaw et al., 2012). Cumulative ART was calculated by adding the weighted ART use variable to reflect years of ART use by the end of the 10-year follow-up period. Optimal ART adherence was defined as taking ≥ 95% of prescribed ART doses at each semiannual visit, as this

has previously been associated with sustained viral suppression (Low-Beer et al., 2000; Paterson et al., 2000). Plasma HIV RNA viral load and CD4+ T-cell counts were measured, semi-annually, using standard laboratory techniques. HIV RNA viral load was subsequently categorized as undetectable (< 200 copies/mL) or detectable (≥ 200 copies/mL; AIDSinfo, 2016). CD4+ T-cell count was categorized as high (≥500 cells/mm3), medium (300 – 500 cells/mm3), or low (< 300 cells/mm3).

Diabetes was dichotomized as having ever been diagnosed with diabetes at any time during follow-up versus no history of diabetes. The Framingham Risk Score (Wilson et al., 1998) was calculated, using the gender-based algorithms, including the following variables: age, total cholesterol, high density lipoprotein (HDL) cholesterol, systolic blood pressure, and smoking status. Therefore, we did not adjust for these variables outside of this risk score. The Framingham Risk Score values range from negative to positive, with negative values indicating low risk and positive values indicating high risk. Body mass index was based on weight and height, and participants were categorized as being underweight (BMI <18.5 kg/m2), normal (18.5-24.9 kg/m2), and overweight (> 24.9 kg/m2).

Psychological. Depressive symptoms were assessed at each semi-annual visit with the Center for Epidemiology Studies Depression Scale (CES-D, Radloff, 1977). Some research has found that utilizing the score of 16 or greater may inflate the rate of depression among PLWH, due to the overlapping somatic symptoms that may be present due to HIV-infection (Kalichmann et al., 2000). Therefore, a score of 23 or greater was considered probable depression. Self-reported illicit drug use was dichotomous and measured at each visit by asking if participants used any of the following: crack or any form of cocaine; uppers (including crystal, methamphetamines, speed, ice); heroin or other opiates.

Social. Race/ethnicity was self-reported and categorized as non-Hispanic white, non-Hispanic black, and other races (Hispanic; Asian/Pacific Islander; Native American/Alaskan). Annual income was self-reported at each visit and categorized, based on natural cut-offs in the data, as < $10,000, $10,000-$30,000, or ≥ $30,000 a year.

To adjust for missing data related to unmeasured variables, percentage of missing follow-up was calculated by summing the number of eligible visits missed, divided by the total number of eligible visits for each individual; wave of enrollment was included in the multivariable models.

Data Analyses

Univariate and bivariate analyses were conducted to assess frequencies and proportions of clinical factors and covariates. To describe patterns of alcohol consumption over time, we conducted group-based trajectory modeling (GBTM). In the first modeling step, we assessed linear patterns of 3-5 groups, as suggested by previous research (Marshall et al., 2015a; Marshall et al., 2015b; Cook, et al., 2013). Goodness-of-fit was assessed at each step using the Akaike information criteria (AIC) and Bayesian information criteria (BIC; smaller the values, better the model), group posterior probabilities (PP≥0.7 is indicative of sufficient internal reliability), and mean model entropy (≥0.7 is optimal; summed PP/number of groups). The PP estimate is the probability that any one group-based trajectory adequately captures the individual patterns. Therefore, an individual pattern was assigned into the group pattern with the highest probability of group membership. Models with PP and/or model entropy values <0.7 were rejected (Andruff et al., 2009). The 95% confidence intervals (CI) of the resulting patterns were used to qualitatively assess the stability of the trajectories. Models with small CIs of trajectories were favored over wide CIs.

Using repeated measures of alcohol consumption and clinical factors, multivariate generalized estimating equations (GEE) were conducted to assess longitudinal associations between clinical factors and moderate (1–7 [14] drinks per week for women [men]) and heavy (>7[14] drinks per week for women[men]) alcohol consumption compared to abstinent/low use (<1 drinks per week), stratified by gender. Clinical factors were considered significantly associated with alcohol consumption at the $p<.05$ level.

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Alcohol Consumption Trajectories

Baseline characteristics by cohort are presented in Table 3-1. A five-group trajectory model emerged as the best fitting model for women (Figure 3-1; model entropy 0.89). Alcohol consumption patterns were labeled as "Abstinent/low" (58%, PP 0.95, very little to no consumption throughout 10-years), "Increasers" (15%, PP 0.86, low/abstinence that increased to moderate consumption), "Decreasers" (7%, PP 0.85, moderate consumption that decreased to low/abstinence), "Moderate" (15%, PP 0.89, moderate consumption throughout 10-years), and "Heavy" (5%, PP 0.92, heavy consumption throughout 10-years). A five-group trajectory model was the best fitting model among men (Figure 2-2; model entropy 0.95): "Abstinent/low" (44% PP 0.98, very little to no alcohol consumption throughout 10-years), "Increasers" (11%, PP 0.92, low/abstinence that increased to moderate consumption), "Decreasers" (14%, PP 0.92, moderate consumption that decreased to low/abstinence), "Moderate" (26%, PP 0.98, moderate consumption throughout 10-years), and "Heavy" (5%, PP 0.96, heavy consumption throughout 10-years). While similar patterns emerged across gender, some differences became apparent. For instance, while women were less likely to drink, in general, membership in the increasers group

was slightly greater among women than men (WIHS 15% vs. MACS 11%). Men were also more likely to be in the decreasers group than women (WIHS 7% vs. MACS 14%).

Multivariate Analysis of Clinical Factors on Alcohol Consumption among Men

Moderate drinking. Bivariate and multivariable analyses are shown in Table 3-2. In multivariate analysis, illicit drug use was associated with 2.21 times the odds for moderate drinking (CI 1.44-3.39, p<.001), compared to abstinent/low use. Those with diabetes had 53% lower odds for moderate drinking (CI 0.30-0.73, p<.001), and those with CD4 count < 300 had 39% lower odds for moderate drinking (compared to ≥ 500; CI 0.40-0.93, p<.05).

Heavy drinking. Bivariate and multivariable analyses are shown in Table 3-4. In multivariable analysis, longitudinal illicit drug use was associated with 2.28 (CI 1.16-4.49, p=.02) times higher odds for heavy drinking. Men diagnosed with diabetes had 67% (CI 0.11-1.01, p=0.05) lower odds for heavy drinking, compared to abstinent/low use.

Multivariate Analysis of Clinical Factors on Alcohol Consumption among Women

Moderate drinking. Bivariate and multivariable analyses are shown in Table 3-3. In multivariate analysis, those with illicit drug use had nearly 3 times higher odds (CI 1.97-4.42, p<.001) for moderate drinking, compared to abstinent/low use. Suboptimal adherence to ART and detectable viral load were associated with 1.21 (CI 1.02-1.44, p<.05) and 1.37 (CI 1.10-1.69, p<.01) times the odds, respectively for moderate drinking. Each unit increase in the Framingham risk score was associated with a 7% increase in odds for moderate drinking (CI 1.50-1.10, p<.001).

Heavy drinking. Bivariate and multivariable analyses are shown in Tables 3-5. In multivariable analysis, longitudinal illicit drug use was associated with over 6 times the odds (CI 3.56-13.4, p<.001) for heavy drinking, compared to abstinent/low use. Women with detectable viral load had 1.55 times the odds for heavy drinking (CI 1.04-2.32, p<0.05). Each increased

year of ART use was associated with 7% lower odds for heavy drinking (CI 0.88-0.98, p<.01). Each unit increase in the Framingham risk score was associated with 12% increase in odds (CI 1.05-1.20, p<.001) for heavy drinking, compared to abstinent/low use.

Discussion

We aimed to describe alcohol consumption trajectories over time and to assess the longitudinal associations between clinical factors and moderate and heavy alcohol consumption. While several alcohol patterns characterized a stable level of consumption (i.e., low/abstinence, moderate, heavy), some patterns also featured shifts in drinking overtime. These shifting patterns add to the existing literature, as other researchers have found mainly stable consumption patterns, likely due to utilizing dichotomous measures of hazardous or heavy drinking (Marshall et al., 2015a; Jacob et al., 2013). This indicates that alcohol consumption should be measured longitudinally to accurately depict exposure. While women tended to drink less, in general, they had slightly higher membership in the increasers trajectory and lower membership in the decreasers trajectory than men. Because these trajectories were increasing to or decreasing from the moderate consumption group, some may consider these results without consequence. However, given the fact that it is relatively unknown whether moderate use confers health benefits or harms among PLWH, these results could suggest that women are a target for prevention/intervention strategies. This is specifically important when considering the lower threshold of number of drinks needed for intoxication (McGinnis et al., 2016) and given the evidence that only 30 drinks per month (ie., moderate use) is associated with increased risk for physical injury and death in this population (Justice et al., 2016), far exceeding risk compared to the 70 drinks per month needed for similar impact among HIV– individuals. Also of significance is the lack of a decreasing trajectory from the heavy pattern across both men and women,

suggesting that once heavy consumption becomes relatively common, this behavior remains overtime.

Results from the multivariate GEE models suggest that there are significant longitudinal clinical associations of moderate and heavy consumption that may help distinguish individuals for prevention and/or early intervention. The most significant associated factors of moderate and heavy alcohol consumption, across both MACS and WIHS cohorts, was longitudinal illicit drug use. This is consistent with cross-sectional (Parsons et al., 2014) and longitudinal (Ruggles et al., 2016) research on the concordance of substance and alcohol use among PLWH. The Framingham risk score was associated with increased odds for moderate and heavy alcohol consumption among women. Diabetes, however, was associated with decreased odds for moderate and heavy drinking among men, which may be due to recommendations from care providers to reduce or stop drinking due to declining health or risk for clinical illness. Conversely, this association could also be indicative of a protective effect of alcohol consumption on diabetes, described in research among the general population (Knott et al., 2015; Pietraszek et al., 2010; Carlsson et al., 2005) Among women, sub-optimal ART adherence was associated with increased odds for moderate alcohol consumption. Furthermore, among women and controlling for ART adherence, having a HIV RNA viral load of 200 or greater was associated with increased odds for membership in the moderate and heavy consumption patterns. This is consistent with previous research indicating that alcohol abuse is linked to HIV progression through alteration of viral infectivity (Deiss et al., 2016), inflammatory biomarkers, immune response, and tissue injury (Monnig et al., 2016; Molina et al., 2014). Conversely, men with lower CD4 count were less likely to be moderate drinkers, compared to the abstinent/low group, suggesting a protective effect.

Limitations

The readers should consider some limitations of the current study. First, alcohol consumption quantity and frequency were assessed via self-report and is subject to recall and social desirability biases, which likely resulted in underestimated reports of alcohol consumption. Second, there are significant demographic differences between the WIHS and MACS cohorts, making direct comparisons of stratified GBTM analyses difficult. It is possible that any differences found may be due to differences in social factors between these cohorts. Third, we restricted our analyses to participants with at least 4 alcohol consumption assessments in order to estimate stable trajectory models. Therefore, it is possible that different trajectories could have emerged had we not excluded these participants. Fourth, those with heavy drinking and comorbidities may have been more likely to drop out of the study or die. This could have affected the results relating to alcohol consumption and clinical conditions, making heavy consumption seem less common among those with diabetes or progressed HIV-infection, when, in fact, there may have been a true positive association. Lastly, GBTM is a semi-parametric and probabilistic model that estimates grouped trajectories of the most similar individual patterns. Therefore, each trajectory does not fully describe the individual-level patterns contained within them and should not be considered absolute.

Conclusions

In summary, the current study added to existing literature on the proportion of HIV+ persons who consume alcohol at specific levels, particularly moderate and heavy consumption. Because alcohol consumption patterns were not limited to characterize only heavy use, and rather were allowed to describe the course of difference levels of use, this study provided information regarding changes in alcohol consumption over time. The results also reveal characteristics that can be used to identify those at risk for moderate and heavy consumption.

The U.S. Preventive Services Task Force recommends that clinicians assess all adults aged 18 years and older for alcohol misuse, and to provide support to reduce risky alcohol consumption (US Preventive Services Task Force, 2013). Further, several screening and brief intervention tools have been developed specifically for clinical use in the general and specific clinical populations (Saitz et al., 2016). In line with these recommendations, clinicians should consider screening all patients for alcohol consumption, particularly if patients report current and past illicit drug use, suboptimal ART adherence, and if patients have detectable viral load. Clinicians could also consider assessing moderate alcohol consumption, as this study found detrimental associations of moderate use on adherence and viral load, particularly among women.

Table 3-1. Baseline characteristics of persons living with HIV by cohort

Baseline Characteristics	WIHS (N=1123) Frequency (Column Percentage)	MACS (N=597)
Race		
White	248 (22)	311 (52)
African American/Black	676 (60)	225 (38)
Other	199 (18)	61 (10)
Age (continuous), mean (SD)	45.0 (7.6)	56.9 (7.7)
Annual Income		
< $10,000	551 (51)	150 (31)
$10,000-$30,000	339 (31)	126 (26)
≥ $30,000	189 (18)	211 (43)
Probable depression		
No	895 (80)	514 (86)
Yes	228 (20)	83 (14)
Illicit drug use		
No	990 (92)	400 (78)
Yes	81 (8)	112 (22)
Ever diagnosed with diabetes		
No	829 (74)	388 (65)
Yes	297 (26)	209 (35)
Body Mass Index		
< 18.5	487 (43)	133 (22)
18.5-24.9	225 (20)	228 (38)
≥ 25.0	411 (37)	236 (40)
HIV RNA Viral Load		
< 200 copies/mL	628 (56)	417 (70)
≥ 200 copies/mL	495 (44)	180 (30)
CD4+ T cell count		
≥ 500 cells/mm^3	443 (39)	264 (44)
300-500 cells/mm^3	323 (29)	157 (26)
< 300 cells/mm^3	357 (32)	176 (30)
HIV ART Adherence		
< 95%	514 (46)	163 (32)
≥ 95%	609 (54)	353 (68)
Cumulative ART exposure, mean (SD), years	12.1 (5.0)	9.4 (4.0)
Framingham Risk Score, mean (SD)	8.4 (6.0)	11.1 (3.3)

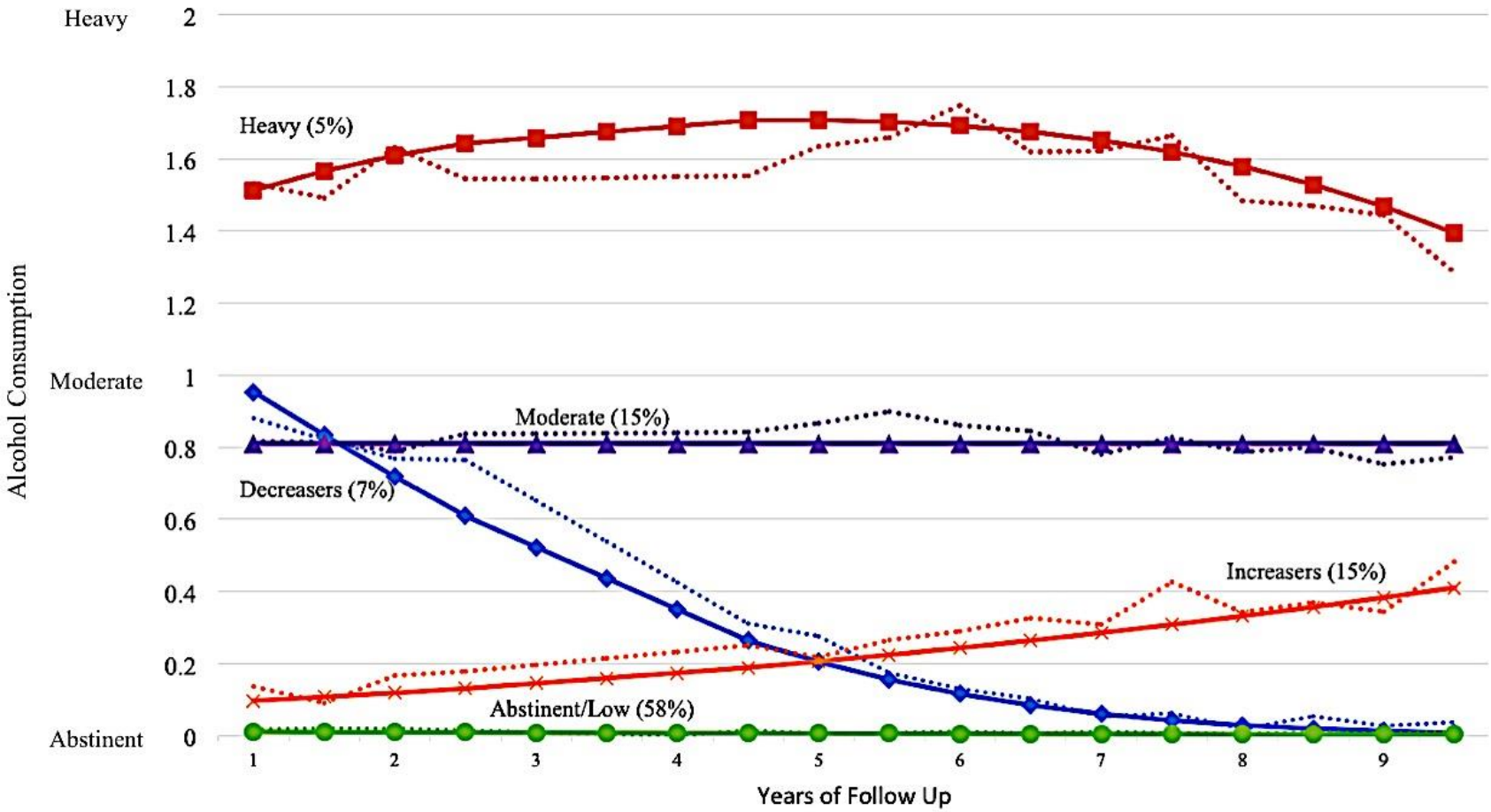

Figure 3-1. Trajectories of alcohol consumption among 1,123 HIV+ women in the Women's Interagency HIV Study. The solid lines represent predicted probabilities of alcohol consumption; the dotted lines represent the actual probabilities of alcohol consumption.

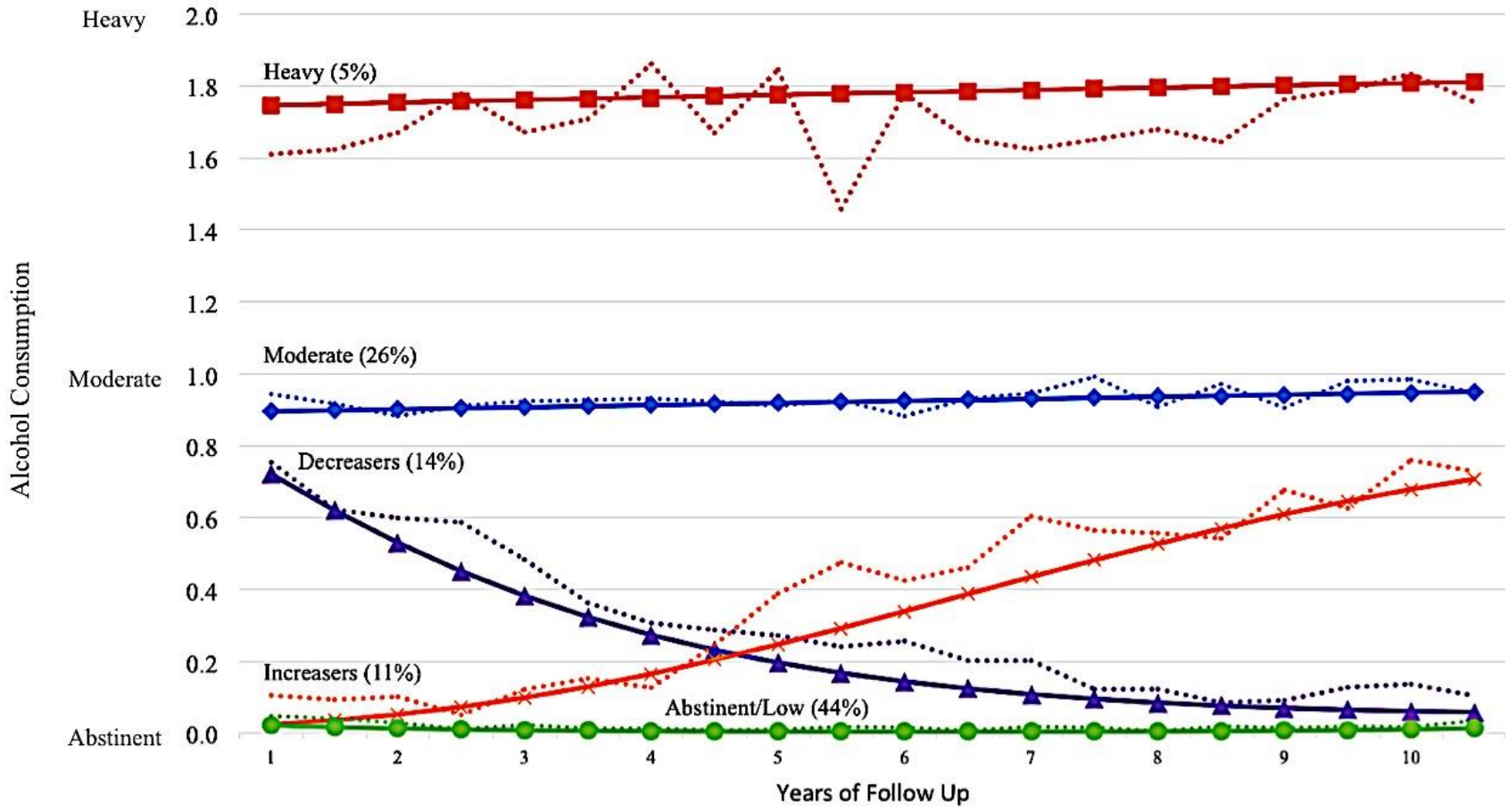

Figure 3-2. Trajectories of alcohol consumption among 597 HIV+ men in the Multicenter AIDS Cohort Study. The solid lines represent predicted probabilities of alcohol consumption; the dotted lines represent the actual probabilities of alcohol consumption.

Table 3-2. Multivariable analysis of associated factors of the moderate alcohol use compared to the low/abstinent alcohol use among men living with HIV

Characteristics	OR	95% CI	P Value	AOR	95% CI	P Value
Race (Ref= White)						
African American/Black	0.39	0.27-0.58	<.001	0.53	0.32-0.90	.02
Other	0.23	0.11-0.11	<.001	0.27	0.12-0.64	<.01
Annual income (Ref = ≥ 30,000)						
< $10,000	0.50	0.32-0.76	<.01	0.78	0.46-1.30	.33
$10,000-$30,000	0.55	0.35-0.84	<.01	0.69	0.43-1.11	.13
BMI status (Ref = Normal)						
Underweight	0.29	0.21-0.41	<.001	0.86	0.58-1.28	.46
Overweight	0.83	0.59-1.17	.30	0.86	0.59-1.26	.45
Diabetes (Ref = No)	0.49	0.33-0.73	<.001	0.47	0.30-0.73	<.001
Probable depression (Ref = No)	1.00	0.71-1.42	.98	0.85	0.58-1.24	.40
Illicit drug use (Ref = No)[a]	1.80	1.22-2.64	<.01	2.21	1.44-3.39	<.001
Suboptimal adherence (Ref ≥ 95%)	0.79	0.56-1.11	.18	1.01	0.68-1.50	.95
CD4+ T-cell (Ref = ≥500)						
300-500	0.79	0.59-1.06	.11	0.80	0.57-1.11	.18
< 300	0.26	0.19-0.38	<.001	0.61	0.40-0.93	.02
Detectable viral load (Ref <200)	0.88	0.64-1.22	.44	0.93	0.64-1.36	.72
Age, years	0.97	0.94-0.99	<.01	0.99	0.95-1.04	.84
Cumulative ART exposure, years	1.11	1.05-1.16	<.001	0.97	0.90-1.05	.53
Framingham risk score	0.95	0.90-1.01	.10	0.98	0.90-1.07	.70

Table 3-3. Multivariable analysis of associated factors of the moderate alcohol use compared to the low/abstinent alcohol use among women living with HIV

Characteristic	OR	95% CI	P Value	AOR	95% CI	P Value
Race (Ref= White)						
African American/Black	1.09	0.74-1.61	.65	0.87	0.59-1.30	.51
Other	0.77	0.46-1.30	.33	0.75	0.43-1.30	.31
Annual income (Ref = ≥ 30,000)						
< $10,000	1.10	0.76-1.59	.60	0.90	0.62-1.29	.56
$10,000-$30,000	1.06	0.73-1.52	.76	1.01	0.70-1.47	.94
BMI status (Ref = Normal)						
Underweight	0.69	0.48-1.00	.05	1.06	0.64-1.76	.80
Overweight	0.83	0.58-1.18	.30	0.94	0.65-1.35	.73
Diabetes (Ref = No)	0.83	0.58-1.18	.29	0.86	0.59-1.25	.43
Probable depression (Ref = No)	1.61	1.26-2.06	<.001	1.17	0.91-1.51	.21
Illicit drug use (Ref = No)	3.93	2.71-5.70	<.001	2.95	1.97-4.42	<.001
Suboptimal adherence (Ref ≥ 95%)	1.06	0.88-1.28	.52	1.21	1.02-1.44	.02
CD4+ T-cell (Ref = ≥500)						
300-500	1.13	0.56-1.03	.31	1.01	0.79-1.28	.95
< 300	0.76	0.56-1.03	.08	0.95	0.68-1.33	.78
Detectable viral load (Ref <200)	2.20	1.78-2.73	<.001	1.37	1.10-1.69	<.01
Age, years	0.98	0.96-1.00	.12	0.96	0.93-0.98	<.01
Cumulative ART exposure, years	0.98	0.96-1.01	.32	0.97	0.94-1.00	.07
Framingham risk score	1.05	1.02-1.07	<.001	1.07	1.04-1.10	<.001

Table 3-4. Multivariable analysis of predictors of the heavy alcohol use compared to the abstinent/low alcohol use among men living with HIV

Characteristics	OR	95% CI	P Value	AOR	95% CI	P Value
Race (Ref= White)						
African American/Black	0.26	0.10-0.64	<.01	0.37	0.10-1.31	.12
Other	0.41	0.13-1.29	.13	0.71	0.19-2.57	.60
Annual income (Ref = ≥ 30,000)						
< $10,000	0.17	0.05-0.54	<.01	0.19	0.05-0.75	.02
$10,000-$30,000	0.24	0.09-0.60	<.01	0.23	0.09-0.59	<.01
BMI status (Ref = Normal)						
Underweight	0.48	0.22-1.03	.06	1.39	0.62-3.10	.42
Overweight	0.67	0.34-1.31	.24	0.53	0.25-1.10	.09
Diabetes (Ref = No)	0.30	0.11-0.79	.01	0.33	0.11-1.01	.05
Probable depression (Ref = No)	1.08	0.55-2.12	.82	1.07	0.53-2.17	.85
Illicit drug use (Ref = No)	2.12	1.12-3.99	.02	2.28	1.16-4.49	.02
Sub-optimal adherence (Ref ≥ 95%)	0.91	0.47-1.76	.78	0.82	0.38-1.79	.62
CD4+ T-cell (Ref = ≥500)						
300-500	1.17	0.68-2.02	.56	1.08	0.59-1.95	.81
< 300	0.53	0.25-1.09	.08	0.91	0.44-1.87	.80
Detectable viral load (Ref <200)	0.92	0.46-1.81	.80	1.03	0.47-2.28	.94
Age, years	0.97	0.92-1.01	.15	1.01	0.93-1.09	.83
Cumulative ART exposure, years	1.05	0.95-1.16	.33	0.91	0.81-1.02	.12
Framingham risk score	0.98	0.89-1.08	.71	1.10	0.94-1.28	.24

Table 3-5. Multivariable analysis of predictors of the heavy alcohol use compared to the abstinent/low alcohol use among women living with HIV

Characteristic	OR	95% CI	P Value	AOR	95% CI	P Value
Race (Ref= White)						
African American/Black	0.99	0.52-1.89	.66	0.99	0.34-1.27	.21
Other	0.38	0.14-1.04	.06	0.29	0.09-0.91	.03
Annual income (Ref = ≥ 30,000)						
< $10,000	0.93	0.50-1.73	.82	0.54	0.30-1.00	.05
$10,000-$30,000	0.89	0.46-1.69	.71	0.74	0.38-1.42	.36
BMI status (Ref = Normal)						
Underweight	0.62	0.32-1.18	.14	0.85	0.31-2.35	.75
Overweight	0.54	0.27-1.08	.08	0.72	0.34-1.50	.38
Diabetes (Ref = No)	0.92	0.49-1.74	.80	1.06	0.52-2.17	.88
Probable depression (Ref = No)	1.90	1.19-3.02	<.01	1.05	0.68-1.64	.81
Illicit drug use (Ref = No)	9.19	5.19-16.2	<.001	6.91	3.56-13.4	<.001
Sub-optimal adherence (Ref ≥ 95%)	1.39	0.97-1.99	.07	1.11	0.85-1.44	.45
CD4+ T-cell (Ref = ≥500)						
300-500	0.99	0.58-1.69	.97	0.80	0.47-1.35	.40
< 300	0.89	0.50-1.59	.70	0.97	0.50-1.85	.92
Detectable viral load (Ref <200)	2.90	1.95-4.32	<.001	1.55	1.04-2.32	.03
Age, years	1.01	0.97-1.05	.71	0.96	0.90-1.01	.15
Cumulative ART exposure, years	0.95	0.90-1.00	.05	0.93	0.88-0.98	<.01
Framingham risk score	1.12	1.06-1.18	<.001	1.12	1.05-1.20	<.001

CHAPTER 4
THE IMPACT OF LONG TERM MODERATE AND HEAVY ALCOHOL CONSUMPTION PATTERNS ON SUBCLINICAL ATHEROSCLEROSIS AMONG PERSONS LIVING WITH HIV

Introduction

Moderate alcohol consumption may be protective against CVD, while heavy use is associated with increased risk for CVD in the general population (Mukamal et al., 2003a, Reynolds et al., 2003; Corrao et al., 2000; Sacco et al., 1999; McElduff and Dobson, 1997). However, the relationship between alcohol consumption and CVD has not been sufficiently examined among PLWH. Heavy alcohol consumption among PLWH is nearly twice the rate compared to uninfected populations (Galvan et al., 2002). Hazardous drinking was reported in 58% of PLWH who received HIV care and consumed alcohol in the past 6 months (Stein et al., 2005). Among HIV infected veterans, 20% and 33% screened positively for hazardous and binge-drinking, respectively, with 32% having been diagnosed with an alcohol use disorder (Conigliaro et al., 2003).

There is little research investigating the association between alcohol consumption and subclinical cardiovascular disease, also known as atherosclerosis. Atherosclerosis is characterized by arterial plaques that may narrow the lumen, decrease blood flow and consequently predispose individuals to acute thrombotic events (National Institutes of Health, 2011). In the general population, light and moderate alcohol use has been cross-sectionally associated with lower risk for carotid artery plaque (Kohsaka et al., 2011) and stiffness (Hougaku et al., 2005), compared to abstinence. Heavy alcohol use, however, has been shown to significantly increase carotid intima medial thickness (cIMT; Zyriax et al., 2010) and stiffness (Hougaku et al., 2005), consistent with a J-curved association found in the literature (Xie et al., 2012; Mukamal et al., 2003b). Similarly, a longitudinal study of 20-year drinking patterns found

that consistent heavy use was associated with a significant increase in cIMT, compared to consistent moderate use (Britton et al., 2016). Other studies have found no significant association between alcohol consumption and cIMT or presence of carotid plaques (Bauer et al., 2013; Zureik et al., 2004). Further, some studies have found significant associations between alcohol consumption and subclinical disease in men, but not in women (Zyriax et al., 2010; Lee et al., 2009; Schminke et al., 2005).

The mechanism by which alcohol consumption is thought to effect cardiovascular health is not well understood, and of great practical importance given the widespread global consumption of alcohol (Freiberg and So-Armah, 2016). Biological and behavioral mechanisms have been proposed to account for the higher burden of CVD among PLWH. First, heavy alcohol consumption and CVD are affected by demographic and psychosocial factors, including age, race/ethnicity, and socioeconomic status (Conen et al., 2009; Galvan et al., 2002), all of which also tend be associated with HIV infection risk. Second, alcohol use is significantly associated with traditional CVD risk factors, including insulin resistance (type II diabetes; Míguez-Burbano et al., 2009), tobacco use (Cook et al., 2013), and illicit drug use (Chitsaz et al., 2013; Cook et al., 2013; Conen et al., 2009). Third, HIV-infection alone increases systemic inflammation (Bahrami et al., 2016; Shrestha et al., 2014) and immune activation (Maniar et al., 2013; Neuhaus et al., 2010; Hsue et al., 2009; Strategies for Management of Antiretroviral Therapy Study Group et al., 2006), pathophysiologic responses that contribute to the risk for CVD (Bahrami et al., 2016, Hsu et al., 2016, Hansson, 2005). Chronic inflammation and immune activation can lead to the breakdown of the endothelial walls of the gastrointestinal tract, a process that leads to microbial translocation which triggers further immune and pro-inflammatory responses (D'Abramo et al., 2014; Klatt el al., 2013; Maniar et al., 2013). While

low level consumption of alcohol may have favorable lipid or antithrombotic effects, low levels of alcohol use have been shown to increase systemic inflammation, as well as risk for microbial translocation (Brenchley and Douek, 2012).

A recent systematic review found the current state of the literature to be limited to mostly cross-sectional studies and/or investigation of vague measures of alcohol use (e.g., any alcohol use, alcohol abuse/dependence history) to characterize risk among majority male HIV infected participants (Kelso et al., 2015). While these studies help us begin to understand the importance of alcohol consumption on cardiovascular health, the study participants were majority male (78-100%). Further, most studies utilize only the medical record to classify diagnosis of clinical CVD, and do not assess early stages of disease development, such as atherosclerosis.

In this study, we assessed the presence of subclinical atherosclerosis (George and Movahed, 2008) by non-invasive carotid artery ultrasound tests. The objective of the current analysis was to assess the association between 10-year patterns of alcohol use and the prevalence and incidence of subclinical atherosclerosis, measured by B-mode carotid artery ultrasound imaging. Specifically, we aimed to 1) test the association between long-term moderate and heavy alcohol use and subclinical atherosclerosis among PLWH, and 2) to explore whether the relationships appeared to differ by gender and between prevalent and incident disease. We hypothesized that long-term moderate and heavy alcohol use would be significantly associated with increased risk for prevalent and incident subclinical atherosclerosis.

Materials and Methods

Study Setting, Selection, and Inclusion Criteria

The Multicenter AIDS Cohort Study (MACS; Dudley et al., 1995; Detels et al., 1992, Kaslow et al., 1987) and Women's Interagency HIV Study (WIHS; Bacon et al., 2005; Barkan et al., 1998) are well-established, national multicenter cohorts of men who have sex with men

(MSM) and of women, respectively, living with or at risk for HIV-infection. Participants from MACS were recruited from the following metropolitan areas: Baltimore, MD, Washington, DC, Chicago, IL, Pittsburgh, PA, Los Angeles, CA. Participants from WIHS were recruited from the following metropolitan areas: Brooklyn and Bronx, NY, Washington, DC, Chicago, IL, Los Angeles and San Francisco, CA. The MACS recruited MSM across three waves, in 1984-1985 (n=4954), 1987-1991 (n=668), and 2001-2003 (n=1350). Women were recruited in WIHS across two waves, in 1994-1995 (n=2625) and 2001-2002 (n=1141). The data were collected through structured interviews, and standardized physical, psychological, and laboratory assessments. HIV status was assessed by enzyme-linked immunosorbent assay (ELISA) with Western blot for confirmation at baseline for HIV+ participants, and semi-annually for HIV- participants. Written informed consent was obtained prior to each semi-annual assessment for both cohorts. The questionnaires are available online for MACS at http://aidscohortstudy.org and for WIHS at https://statepi.jhsph.edu/wihs/wordpress/.

The WIHS cardiovascular sub-study recruited women aged 25 to 60 years, with no history of heart surgery or coronary angioplasty/stent placement before HIV infection (n=1,321); The MACS cardiovascular sub-study recruited men over 40 years of age, under 300lbs, and with no history of heart surgery or coronary angioplasty/stent placement before HIV infection (n=828). The current study focused on those with HIV sero-prevalence at baseline and excluded those who sero-converted (WIHS: n=118; MACS: n=216). For both cohorts, those in the 2001-2002 (MACS 2003) wave of enrollment were not included in the prevalence analysis (taking place in 2004-2006), since there was not opportunity to measure 10-year alcohol consumption at that point, reducing the sample of baseline assessment by n=403 in WIHS and n=264 in MACS. However, those that were in the 2001-2003 wave of enrollment who had a baseline (and no

prevalent disease) and follow-up assessment were included for the incidence analysis (taking place in 2011-2013), since 10-year alcohol consumption data were available by that time point. Therefore, those in the prevalence and incident analysis are not directly comparable. The final sample sizes were n=800 in WIHS and n=348 in MACS for prevalent carotid lesions (at least one ultrasound assessment) and n=512 in WIHS and n=324 in MACS for incident lesions (two ultrasound assessments). The median person-years of follow-up between 1994-2014 was 16.7 years (interquartile range [IQR]: 16.0-18.5 years) for WIHS participants and 12.4 years (IQR: 10.0-16.5 years) for MACS participants. All MACS and WIHS participants provided written informed consent for overall study participation, and this specific analysis was approved by the Institutional Review Board at the University of Florida.

Data Collection

In addition to the standard data collection for the MACS and WIHS, participants in the cardiovascular sub-studies underwent high-resolution B-mode carotid artery ultrasounds of 6 locations in the right carotid artery (the near and fall walls of the common carotid artery [CCA], carotid bifurcation, and internal carotid artery [ICA]; Hodis et al., 2001), using a standardized protocol across study sites (Kaplan et al., 2008). Quality control and reliability of the carotid artery ultrasound measurement was performed among a subset of WIHS and MACS participants and was found to have high intraclass correlations (ICC) in both WIHS (variation coefficient = 1.8%; ICC = 0.98) and MACS (variation coefficient = 1.0%; ICC=0.99; Kaplan et al., 2008).

Main outcome measure

Subclinical atherosclerosis was defined as the presence of an arterial lesion or plaque, which was a focal carotid intima-media thickness over 1.5mm (Stein et al., 2008) and was measured up to 2 times from 2004-2013. Two outcomes of interest were considered: prevalent and incident subclinical atherosclerosis. Lesions or plaques present at baseline assessment were

considered prevalent cases. Participants that screened negative for lesions or plaques at the baseline assessment, but positive at the follow-up were considered incident cases, therefore those who had prevalent disease or who did not have 2 carotid ultrasound assessments were not included in the assessment of incident atherosclerosis.

Independent variable

Alcohol consumption was self-reported by asking about the average frequency (number of days per week) and quantity (number of drinks per drinking day) of use. The average number of drinks per week was calculated by multiplying the frequency by the quantity. Number of drinks per week were capped at 14 for women and 21 for men in accordance with the definition of hazardous alcohol use (Reid et al., 1999). For example, women that reported > 14 drinks per week were given a value of 14.

Covariates

All covariates were chosen based on our conceptual model (Figure 4-1) and were measured at the time of baseline and follow-up assessments. Age was assessed in years, using participants' self-reported date of birth. Self-reported race was categorized as white, black, and Asian/Pacific Islander or Native American/Alaskan. Self-reported smoking was assessed in number of packs smoked using standardized categories: less than half a pack per day; at least half a pack but less than one pack per day; at least one but less than two packs per day; two or more packs per day. Cumulative pack-years were calculated to determine the average pack, multiplied by 0.5 to reflect the semi-annual visits, and summed across the years prior to the carotid artery ultrasound assessments. Self-reported illicit drug use included any of the following: crack or any form of cocaine; uppers (including crystal, methamphetamines, speed, ice); heroin or other opiates and was dichotomized. Plasma HIV RNA viral load was measured using standard laboratory techniques. HIV RNA viral load was categorized as < 200 copies/mL

or ≥ 200 copies/mL. Cardiovascular risk factors included body mass index (BMI), hypertension (blood pressure ≥ 140/90 or if the participant had been told by a doctor that they have hypertension) and diabetes (dichotomized as having been diagnosed with diabetes versus no history of diabetes).

Data Analyses

Group-based trajectory models

To describe patterns of alcohol consumption over time, we conducted group-based trajectory models (GBTM). In the first modeling step, we assessed linear patterns of 3-5 groups, as suggested by previous research (Marshall et al., 2015a; Marshall et al., 2015b; Cook et al., 2013). Goodness-of-fit was assessed at each step using the Akaike information criteria and Bayesian information criteria (smaller the values, better the model), group posterior probabilities (PP≥0.7 is indicative of sufficient internal reliability), and mean model entropy (≥0.7 is optimal; summed PP/number of groups). The PP estimate is the probability that any one group-based trajectory adequately captures the individual patterns. Therefore, an individual pattern was assigned into the group pattern with the highest probability of group membership. Models with PP and/or model entropy values <0.7 were rejected (Andruff et al., 2009). The 95% confidence intervals (CI) of the resulting patterns were used to qualitatively assess the stability of the trajectories. Models with small CIs of trajectories were favored over wide CIs. Separately for each cohort, a group-based trajectory modeling was conducted to describe 10-year drinking patterns prior to the measurement of prevalent and incident atherosclerosis (Figure 4-2). Trajectories that described weekly drinking of 1-7 drinks for women and 1-14 drinks for men were collapsed and labeled as “Moderate” when applicable, and those that described consistent weekly drinking of > 7 drinks for women and >14 drinks for men were labeled as “Heavy”. Age-

adjusted prevalence and incidence was calculated, stratified by gender and combined, using standardized population data (United States Census Bureau, 2000).

Multivariable logistic regression models

Crude and adjusted associations between alcohol consumption patterns and the prevalence and incidence of subclinical atherosclerosis were conducted using separate logistic regression models, first stratified by gender and then with cohorts combined. Multivariable adjustment of the aforementioned covariates was conducted in all logistic regression models in a stepwise fashion, with demographic factors (i.e., age, race/ethnicity, gender when applicable) being added first, followed by substance use (i.e., pack years, illicit drug use), CVD related risk factors (BMI, hypertension, diabetes, hepatitis C), and HIV RNA viral load. Compared to the lowest alcohol consumption pattern, other alcohol consumption patterns were considered statistically significantly associated with prevalent and incident subclinical atherosclerosis at the p-value < .05 level.

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Sample characteristics by cohort at baseline and follow-up are presented in Table 4-1. There were 800 HIV+ women and 348 HIV+ men at baseline. Median age at baseline was 45.8 (IQR 40.4-50.5) years in women and 56.1 (IQR 50.2-61.4) years in men. Women were more likely to be of black race than men (58% vs. 25%). Men were more likely to report illicit drugs use (19% vs. 9%) and had higher cumulative pack-years (3.9 vs. 2.6) than women. Body mass index was higher among women (28.1 vs. 25.6), while hypertension (40% vs. 24%) and diabetes (34% vs. 26%) was more likely in men than women. Hepatitis C co-infection was higher among women than men (27% vs. 13%). At baseline, men were more likely to have suppressed viral load (84% vs. 52%) compared to women.

There were 512 HIV+ women and 324 HIV+ men who met study criteria at follow-up (Table 4-1). Median age (years) at follow-up was about 51 in women and 65 in men. Women were more likely to be of black race than men (63% vs. 43%). Men were more likely to report illicit drugs use (16% vs. 7%). Cumulative pack-years (women 2.6 [IQR 0.0-4.1]; men 2.1 [IQR 0.0-2.1]) and Hepatitis C co-infection (women 15%; men 16) were similar by gender. Body mass index was higher among women (30.7 vs. 26.6), while hypertension (45% vs. 30%) and diabetes (37% vs. 26%) was more likely in men than women. At follow-up, men were more likely to have suppressed viral load (89% vs. 72%) compared to women.

Prevalent Subclinical Atherosclerosis

Prevalent subclinical atherosclerosis was identified in 16% (n=125; age-adjusted prevalence 14.1/100) of women and 26% (n=90; 25.0/100) of men. The prevalence for subclinical atherosclerosis (Table 4-2) was the highest among men in the abstinent/low alcohol use pattern (31.1/100), followed by heavy use (28.4/100) and moderate use (24.3/100). Among women, prevalence was highest in the abstinent/low alcohol use pattern (15.6/100), followed by moderate use (15.0/100) and heavy use (12.8/100). When the WIHS and MACS cohorts were combined, the highest prevalence for subclinical atherosclerosis was in the heavy alcohol use group (16.3/100), followed by the abstinent/low use group (15.9/100), and the moderate use group (15.2/100).

In analysis of alcohol use patterns at baseline, a four-group trajectory model emerged as the best fitting model for women (Figure 4-3, Panel A; model entropy 0.94) and men (Figure 4-3, Panel B; model entropy 0.97). Alcohol consumption patterns included “Abstinent/Low” (women 35%; men 16%, little to no consumption throughout 10-years), “Moderate” (women 59%; men 76%, moderate consumption throughout 10-years) and “Heavy” (women 6%; men 8% heavy consumption throughout 10-years).

Crude and adjusted odds ratios (AOR) of alcohol consumption patterns on prevalent subclinical atherosclerosis are presented in Table 4-3. Long-term heavy alcohol use was not statistically significantly associated with increased risk for prevalent subclinical atherosclerosis in women (AOR 0.86, CI 0.38-1.97, p=.73) or men (AOR 1.16, CI 0.38-3.54, p=.79), compared to abstinence. While moderate alcohol use tended toward a protective effect on prevalent subclinical atherosclerosis in women (AOR 0.71, CI 0.45-1.10, p=.12), a similar association was not found in men (AOR 1.08, CI 0.51-2.28, p=.84), compared to abstinence and after controlling for race, age, pack-years, illicit drug use, BMI, hypertension, diabetes, hepatitis c co-infection, and suppressed viral load. In analysis that combined both women and men, heavy alcohol consumption was not statistically significantly associated with prevalent subclinical atherosclerosis (AOR 0.99, CI 0.52-1.88, p=.97), while moderate alcohol consumption tended toward a protective effect, with 22% lower odds for prevalent subclinical disease (CI 0.54-1.13, p=.20), compared to abstinent/low use.

Incident Subclinical Atherosclerosis

Incident subclinical atherosclerosis was detected in 12% (n=61; incidence 13.0/100) of women and 18% (n=58; incidence 16.6/100) of men. The incidence for subclinical atherosclerosis (Table 4-2) was the highest among men in the abstinent/low alcohol use pattern (36.6/100), followed by heavy use (24.0/100) and moderate use (13.4/100). Among women, incidence was highest in the abstinent/low alcohol use pattern (15.3/100), followed by heavy use (11.6/100) and moderate use (8.6/100). When the WIHS and MACS cohorts were combined, the highest incidence for subclinical atherosclerosis was in the abstinent/low alcohol use group (15.9/100), followed by the heavy use group (15.0/100), and the moderate use group (10.1/100).

A three-group trajectory model emerged as the best fitting model for women (Figure 4-3, Panel C; model entropy 0.98) and men (Figure 4-3, Panel D; model entropy 0.98). Alcohol

consumption patterns included “Abstinent/low” (WIHS 46%; MACS 19%, very little to no consumption throughout 10-years), “Moderate” (WIHS 45%; MACS 72%, moderate consumption throughout 10-years) and “Heavy” (WIHS 9%; MACS 9%, heavy consumption throughout 10-years) alcohol consumption.

Crude and adjusted odds ratios of alcohol consumption patterns on incident subclinical atherosclerosis are presented in Table 4-4. Long-term heavy alcohol use was not statistically significantly associated with increased risk for incident subclinical atherosclerosis in women (AOR 1.08, CI 0.39-3.01, p=.87) and men (AOR 1.40, CI 0.46-4.26, p=.55). While moderate alcohol use leaned toward a protective effect on incident subclinical atherosclerosis in men (AOR 0.53, CI 0.25-1.13, p=.10), a similar association was not found in women (AOR 1.05, CI 0.57-1.92, p=.88), after controlling for race, age, pack-years, illicit drug use, BMI, hypertension, diabetes, hepatitis c co-infection, and suppressed viral load. In analysis that combined both cohorts, heavy (AOR 1.28, CI 0.63-2.62, p=.49) and moderate (AOR 0.79, CI 0.50-1.27, p=.34) alcohol consumption were not statistically significantly associated with incident subclinical atherosclerosis, compared to abstinent/low use.

Discussion

We aimed to assess the association between 10-year patterns of alcohol use and the prevalence and incidence of atherosclerosis, measured by B-mode carotid artery ultrasound. Specifically, we aimed to test the general assumption that moderate alcohol consumption is protective to cardiovascular health among PLWH. Contrary to our hypothesis, long-term heavy alcohol use was not statistically significantly associated with prevalent or incident atherosclerosis. These results are contrary to previous studies that have demonstrated an association between heavy alcohol use and subclinical atherosclerosis in the general population (Xie et al., 2012; Zyriax et al., 2010; Hougaku et al., 2005; Mukamal et al., 2003b) and extent

literature finding positive associations between heavy alcohol use and clinical cardiovascular disease among PLWH (Freiberg et al., 2010; Corral et al., 2009; Justice et al., 2008). However, this finding is consistent with recent studies finding no association between heavy drinking and cardiovascular disease among PLWH (Kelly et al., 2016; Wandeler et al., 2016; Womack el al., 2014) and subclinical atherosclerosis in the general population (Kim et al., 2014; Bauer et al., 2013; Zureik et al., 2004). It is possible that heavy alcohol use is a contributor to risk for clinical cardiovascular disease, but less predictive at the developmental stages of atherosclerosis. An additional explanation could be that abstinent/low drinkers had a history of heavy drinking that is not captured in the 10-year patterns. If past heavy drinking conferred increased risk more than 10-years later, then the effect of current 10-year patterns of heavy drinking could be attenuated when compared to the current abstinent/low drinkers.

We found that long-term moderate alcohol use leaned toward lower odds for prevalent (in women) and incident (in men) atherosclerosis. While these estimates did not meet statistical significance, this finding is consistent with other research indicating a J-curved relationship between alcohol consumption and subclinical atherosclerosis in the general population (Kohsaka et al., 2011; Hougaku et al., 2005) and extent research on clinical disease in the general population (Mukamal et al., 2003a, Reynolds et al., 2003; Corrao et al., 2000; McElduff and Dobson, 1997, Sacco et al., 1999) and among PLWH (Wandeler et al., 2016, Carrieri et al., 2012, Schminke et al., 2005).

Limitations

The readers should consider some limitations of the current study. First, alcohol consumption quantity and frequency were assessed via self-report and is subject to recall and social desirability biases, resulting in underestimated reports of alcohol consumption. However, this method has been established as a reliable and valid approach to alcohol use assessment (Del

Boca and Darkes, 2003). Second, because we used carotid artery ultrasound, these results can only be generalized to disease within the carotid artery and may not extend to of plaque or lesions outside of this area. Carotid artery ultrasound also does not capture all mechanisms that are involved in atherothrombotic events, being most strongly associated with blood pressure levels (Sander et al., 2000) and bearing little relationship with coagulation (Sosef et al., 1994) or platelet activity (De Luca G et al., 2010), for example. However, research has found presence of plaque or lesions within the carotid artery to be highly correlated to subclinical disease in other vascular territories when compared to other methods that detect low to no disease (Lester et al., 2009, Davis et al., 1999). While we did not aim to investigate clinical CVD, subclinical atherosclerosis is a proximal indicator of later clinical manifestations of CVD, such as myocardial infarction and stroke. Third, there are significant demographic differences between the WIHS and MACS cohorts, making direct comparisons of stratified analyses difficult. Because of these differences, we carefully controlled for variables related to cardiovascular risk. Fourth, GBTM is a semi-parametric and probabilistic model that estimates grouped trajectories of the most similar individual patterns. Therefore, each trajectory group does not fully describe the individual-level patterns contained within them and should not be considered absolute. Further, we restricted our analyses to participants with at least 4 alcohol consumption assessments in order to estimate trajectory models. Therefore, it is possible that different trajectories could have emerged had we not excluded these participants.

Conclusions

In summary, the current study adds to the literature on the effect of longitudinal alcohol consumption on CVD among PLWH, by focusing on early subclinical manifestations of atherosclerosis. This study provides important new information regarding the specific effect of moderate alcohol use, and thus helps fill the gap in this area of alcohol research. Future research

should continue to investigate the effect of alcohol use on atherosclerosis and interactions with other significant factors, such as mental health issues, social support, and antiretroviral treatments. It is possible, that through this continued research, we may be able to identify subgroups of drinkers that are a greater risk for cardiovascular disease, by which tailored interventions can target. Further, validation of the J-curve association could focus on the proposed risk mechanisms between alcohol consumption and cardiovascular health. For example, if moderate consumption is protective, we would expect decrease in pro-inflammatory and cardiac biomarkers.

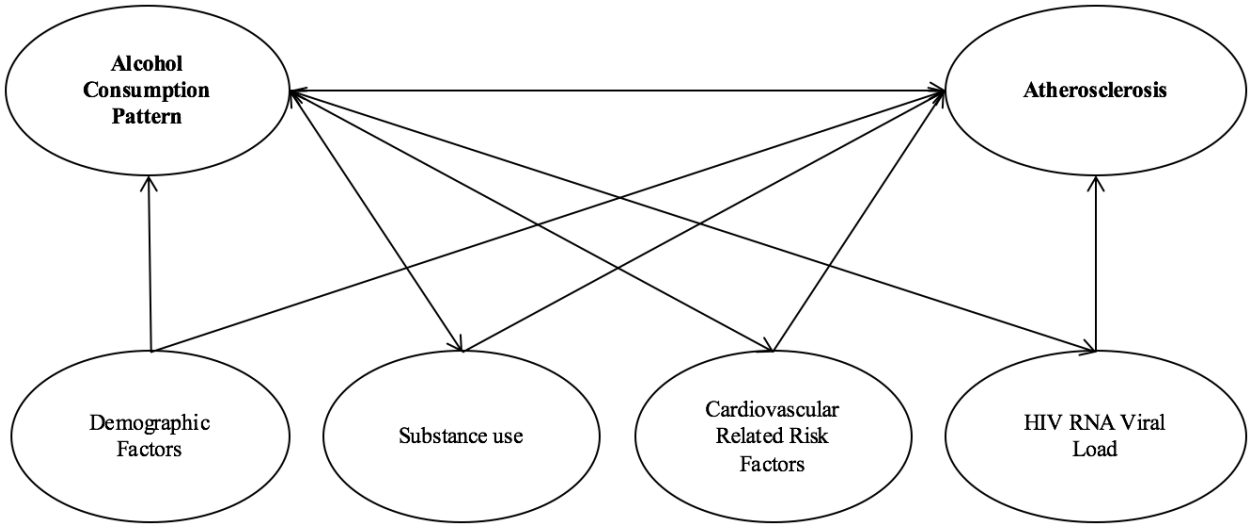

Figure 4-1. Conceptual model for the association between alcohol consumption and atherosclerosis and confounding factors

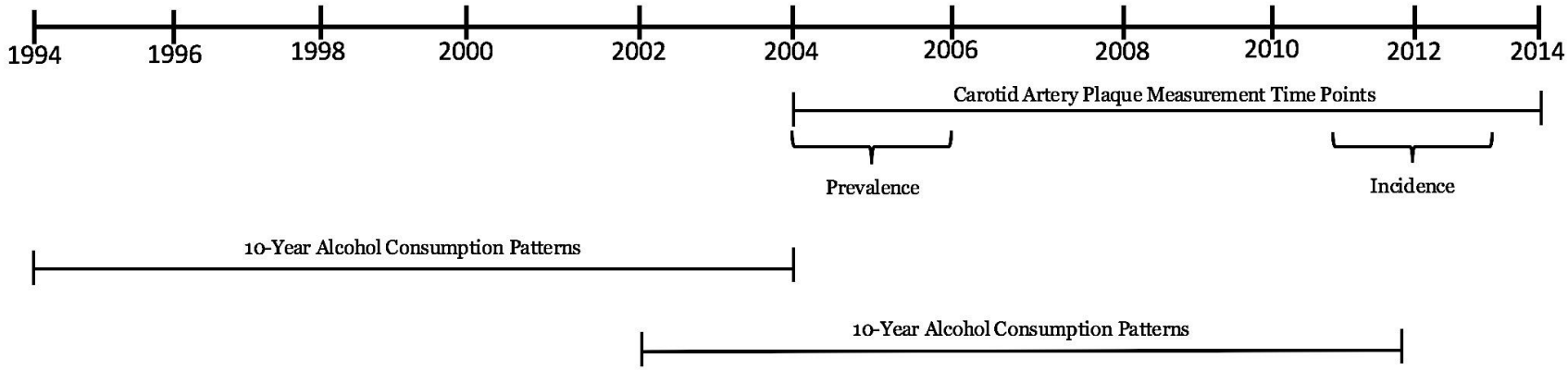

Figure 4-2. Timeline for 10-year trajectory models prior to prevalent and incident subclinical atherosclerosis

Table 4-1. Sample characteristics of women and men living with HIV by cohort

	Baseline		Follow-up	
	WIHS (N=800)	MACS (N=348)	WIHS (N = 512)	MACS (N=324)
Race				
White	139 (17)	229 (68)	101 (20)	139 (43)
Black	468 (58)	87 (25)	322 (63)	140 (43)
Other (Asian, Native American, etc.)	193 (24)	32 (9)	89 (17)	45 (14)
Age, mean (IQR)	45.8 (40.4-50.5)	56.1 (50.2-61.4)	50.7 (45.6-55.0)	65.1 (60.5-70.0)
Smoking pack-years, mean (IQR)	2.7 (0.0-4.5)	3.9 (0.0-4.9)	2.6 (0.0-4.1)	2.1 (0.0-2.1)
Illicit drug use				
No	729 (91)	282 (81)	478 (93)	273 (84)
Yes	71 (9)	66 (19)	34 (7)	51 (16)
Body Mass Index, mean (IQR)	28.1 (22.9-31.3)	25.6 (22.9-27.4)	30.7 (26.4-34.5)	26.6 (23.3-29.0)
Hypertension				
No	608 (76)	208 (60)	360 (70)	179 (55)
Yes	192 (24)	140 (40)	152 (30)	145 (45)
Diabetes				
No	596 (74)	229 (66)	378 (74)	205 (63)
Yes	204 (26)	119 (34)	134 (26)	119 (37)
Hepatitis C status				
Negative	583 (73)	304 (87)	433 (85)	271 (84)
Positive	217 (27)	44 (13)	79 (15)	53 (16)
HIV RNA Viral Load				
< 200 copies/mL	418 (52)	291 (84)	368 (72)	289 (89)
≥ 200 copies/mL	382 (48)	57 (16)	144 (28)	35 (11)
Cross-sectional alcohol consumption				
Abstinence-Low (<1 drink/week)	513 (64)	213 (61)	405 (79)	248 (76)
Moderate (1-7 drinks/week)	217 (27)	117 (34)	88 (17)	64 (20)
Heavy (>7 drinks/week)	70 (9)	18 (5)	19 (4)	12 (4)
10-year alcohol consumption pattern				
Abstinent-Low	279 (35)	55 (16)	236 (46)	63 (19)
Moderate	472 (59)	265 (76)	226 (45)	233 (72)
Heavy	49 (6)	28 (8)	47 (9)	28 (9)
Prevalent lesions, baseline				
No	675 (84)	258 (74)		
Yes	125 (16)	90 (26)		
Incident lesions, follow-up				
No			451 (88)	266 (82)
Yes			61 (12)	58 (18)

WIHS, Women's Interagency HIV Study; MACS, Multicenter AIDS Cohort Study; IQR, interquartile range

Table 4-2. Age-adjusted prevalence and incidence of subclinical atherosclerosis by alcohol consumption patterns

Alcohol use pattern	N (Prevalence)	N (Incidence)
MACS		
Abstinent/low	52 (31.1/100)	63 (36.6/100)
Moderate	253 (24.3/100)	233 (13.4/100)
Heavy	28 (28.4/100)	28 (24.0/100)
WIHS		
Abstinent/low	279 (15.6/100)	236 (15.3/100)
Moderate	406 (15.0/100)	226 (8.6/100)
Heavy	49 (12.8/100)	47 (11.6/100)
Total		
Abstinent	334 (15.9/100)	299 (15.9/100)
Moderate	737 (15.2/100)	459 (10.1/100)
Heavy	77 (16.3/100)	75 (15.0/100)

WIHS, Women's Interagency HIV Study; MACS, Multicenter AIDS Cohort Study

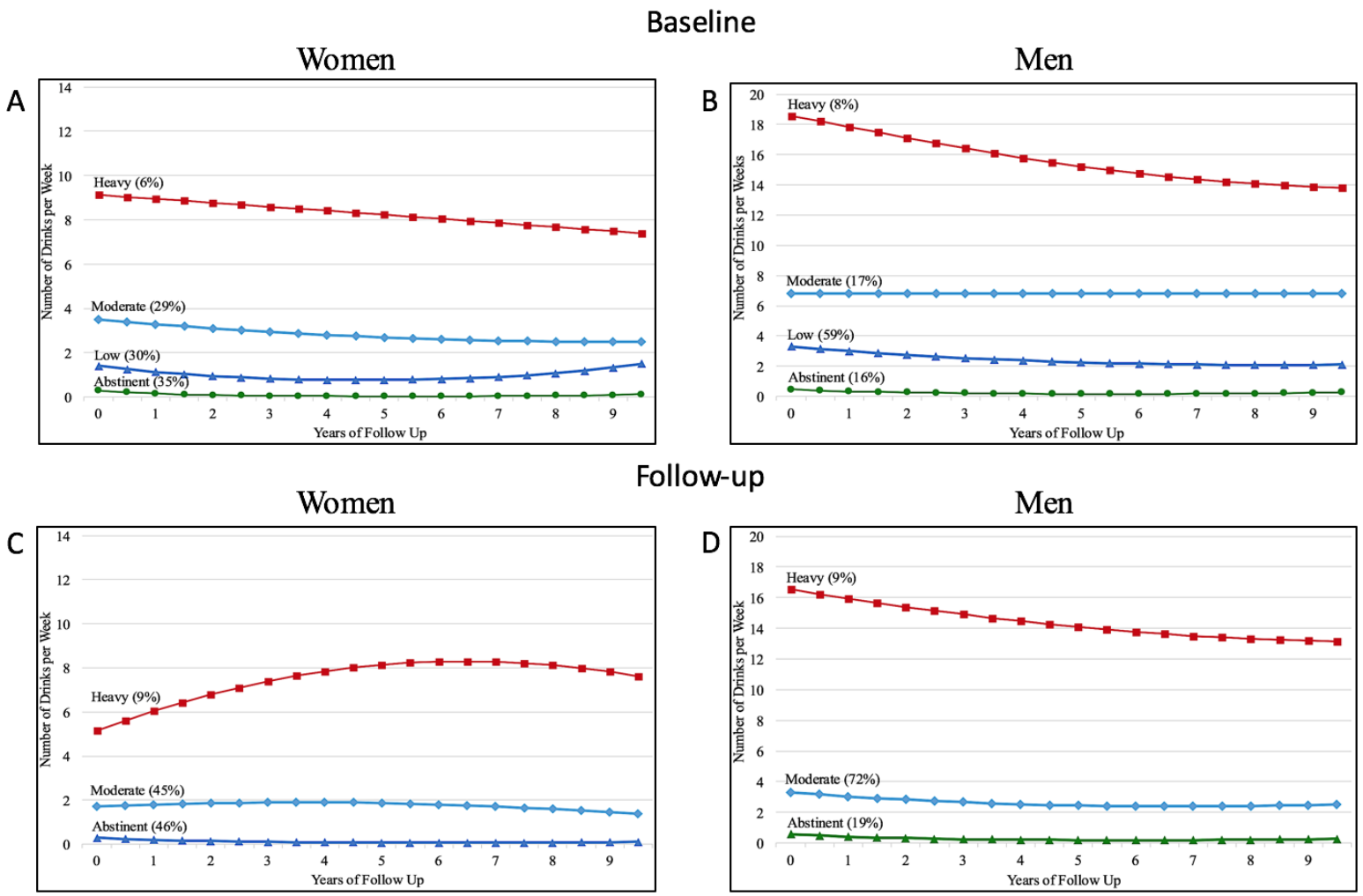

Figure 4-3. 10-year alcohol consumption trajectories by cohort. Panel A: Alcohol consumption patterns in women prior to baseline carotid artery ultrasound; Panel B: Alcohol consumption patterns in men prior to baseline carotid artery ultrasound; Panel C: Alcohol consumption patterns in women prior to follow-up carotid artery ultrasound; Panel D: Alcohol consumption patterns in men prior to follow-up carotid artery ultrasound

Table 4-3. Association between 10-year alcohol consumption patterns and prevalent subclinical atherosclerosis, overall and by cohort

	Women's Interagency HIV Study (WIHS)				Multicenter AIDS Cohort Study (MACS)			
	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value
Alcohol Consumption Patterns								
Abstinent	REF		REF		REF		REF	
Low-Moderate	0.78 (0.52-1.17)	.23	0.71 (0.45-1.10)	.12	0.99 (0.51-1.93)	.98	1.08 (0.51-2.28)	.84
Heavy	1.39 (0.66-2.92)	.38	0.86 (0.38-1.97)	.73	1.39 (0.51-3.77)	.52	1.16 (0.38-3.54)	.79

[a] Controlled for race, age, illicit drug use, pack years of cigarette use, body mass index, diabetes, hypertension, hepatitis c co-infection, and suppressed viral load

Table 4-3. Continued

	Combined			
	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value
Alcohol Consumption Patterns				
Abstinent	REF		REF	
Low-Moderate	0.97 (0.69-1.35)	.84	0.78 (0.54-1.13)	.20
Heavy	1.54 (0.86-2.75)	.14	0.99 (0.52-1.88)	.97

[a] Controlled for gender, race, age, illicit drug use, pack years of cigarette use, body mass index, diabetes, hypertension, hepatitis c co-infection, and suppressed viral load

Table 4-4. Association between 10-year alcohol consumption patterns and incident subclinical atherosclerosis, overall and by cohort

	Women's Interagency HIV Study (WIHS)				Multicenter AIDS Cohort Study (MACS)			
	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value
Alcohol Consumption Patterns								
Abstinent/Low	REF		REF		REF		REF	
Moderate	0.95 (0.54-1.68)	.86	1.05 (0.57-1.92)	.88	0.50 (0.26-0.98)	.04	0.53 (0.25-1.13)	.10
Heavy	1.30 (0.52-3.18)	.56	1.08 (0.39-3.01)	.87	1.17 (0.43-3.18)	.75	1.40 (0.46-4.26)	.55

[a] Controlled for race, age, body mass index, diabetes, hypertension, illicit drug use, pack years of cigarette use, and suppressed viral load

Table 4-4. Continued

	Combined			
	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value
Alcohol Consumption Patterns				
Abstinent/Low			REF	
Moderate	0.86 (0.57-1.32)	.50	0.79 (0.50-1.27)	.34
Heavy	1.45 (0.76-2.77)	.26	1.28 (0.63-2.62)	.49

[a] Controlled for gender, race, age, body mass index, diabetes, hypertension, illicit drug use, pack years of cigarette use, and suppressed viral load

CHAPTER 5
THE IMPACT OF 10-YEAR PAST AND CURRENT ALCOHOL CONSUMPTION PATTERNS ON EARLY PROGRESSION OF ATHEROSCLEROSIS AMONG PERSONS LIVING WITH HIV

Introduction

Persons living with HIV (PLWH) have higher odds for subclinical atherosclerosis, compared to uninfected controls (Hanna et al., 2015; Hsue et al., 2012; Grunfeld et al., 2009), after adjusting for standard metabolic and HIV-related risk factors. This suggests that there are indicators outside of the traditional risk factor framework that are important contributors to cardiovascular health, such as alcohol consumption. A J-curve has been observed in epidemiologic studies of alcohol use and cardiovascular disease (CVD) morbidity and mortality in the general population (Mukamal et al., 2003a; Reynolds et al., 2003; Corrao et al., 2000; McElduff and Dobson, 1997; Sacco et al., 1999). Previous research has focused predominantly on the association between alcohol consumption and clinical endpoints (myocardial infarction, stroke, heart attack) and less on intermediate measures of cardiovascular disease development or subclinical atherosclerosis, such as carotid intima media thickness (cIMT). Carotid intima media thickness, measured by high resolution B-mode ultrasound, is the thickness (mm) of the inner and middle layers of the carotid artery. Further, the relationship between alcohol consumption and subclinical atherosclerosis has not been sufficiently examined among PLWH.

The studies that do examine the relationship between alcohol consumption and subclinical atherosclerosis among the general population yield inconsistent findings. Some studies have found a protective effect of moderate alcohol consumption on subclinical atherosclerosis, compared to abstinence (Kohsaka et al., 2011; Hougaku et al., 2005), while others find alcohol consumption at any level to be a risk factor (Zyriax et al., 2010), or not associated with subclinical atherosclerosis (Tofferi, et al., 2004). Further, some studies have

found significant associations between alcohol consumption and subclinical disease in men, but not in women (Kim et al., 2014; Zyriax et al., 2010; Lee et al., 2009; Schminke et al., 2005). Aside from the general lack of research assessing the association between alcohol consumption and subclinical atherosclerosis among PLWH, there are no studies investigating the effects of past longitudinal and current alcohol consumption patterns on progression of cIMT as an indicator of CVD disease development.

The objective of the current analysis was to assess the association between patterns of alcohol consumption and cIMT progression among PLWH. Specifically, we aimed to 1) assess the relationship of past (10-year) and current (6-month) alcohol consumption patterns to cIMT progression among PLWH, and 2) to explore whether the relationships appeared to differ by gender. We hypothesized that past long-term alcohol exposure would be more significantly associated with cIMT progression versus current short-term alcohol exposure. In general, however we expected that moderate alcohol consumption would be associated with a protective effect (lower cIMT level over time) and heavy alcohol consumption would be associated with a harmful effect (higher cIMT lever over time) on cIMT.

Methods

Study Setting, Selection, and Inclusion Criteria

The Multicenter AIDS Cohort Study (MACS; Dudley et al., 1995; Detels et al., 1992; Kaslow et al., 1987) and Women's Interagency HIV Study (WIHS; Bacon et al., 2005; Barkan et al., 1998) are well-established, national multicenter cohorts of men who have sex with men (MSM) and of women, respectively, living with or at risk for HIV-infection. Participants from MACS were recruited from the following metropolitan areas: Baltimore, MD, Washington, DC, Chicago, IL, Pittsburgh, PA, Los Angeles, CA. Participants from WIHS were recruited from the following metropolitan areas: Brooklyn and Bronx, NY, Washington, DC, Chicago, IL, Los

Angeles and San Francisco, CA. The MACS recruited MSM across three waves, in 1984-1985 (n=4954), 1987-1991 (n=668), and 2001-2003 (n=1350). Women were recruited in WIHS across two waves, in 1994-1995 (n=2625) and 2001-2002 (n=1141). The data were collected through structured interviews, and standardized physical, psychological, and laboratory assessments. HIV status was assessed by enzyme-linked immunosorbent assay (ELISA) with Western blot for confirmation at baseline for HIV+ participants, and semi-annually for HIV- participants. HIV sero-conversion was confirmed by testing HIV- participants at each semi-annual visit. Written informed consent was obtained prior to each semi-annual assessment for both cohorts. The questionnaires are available online for MACS at http://aidscohortstudy.org and for WIHS at https://statepi.jhsph.edu/wihs/wordpress/.

The WIHS cardiovascular sub-study recruited women aged 25 to 60 years, with no history of heart surgery or coronary angioplasty/stent placement before HIV infection; The MACS cardiovascular sub-study recruited men over 40 years of age, under 300lbs, and with no history of heart surgery or coronary angioplasty/stent placement before HIV infection. For the current analysis we excluded those who seroconverted during the study and those with less than 4 alcohol consumption assessments. The median person-years of follow-up between 1994-2014 were 16.7 years (interquartile range [IQR]: 16.0-18.5 years) for WIHS participants and 12.4 years (IQR: 10.0-16.5 years) for MACS participants. All MACS and WIHS participants provided written informed consent for overall study participation. The Institutional Review Board at the University of Florida approved this specific analysis.

Data Collection

In addition to the standard data collection for the MACS and WIHS, participants in the cardiovascular sub-studies underwent high-resolution B-mode carotid artery ultrasounds of 6 locations in the right carotid artery (the near and fall walls of the common carotid artery [CCA],

carotid bifurcation, and internal carotid artery [ICA]; Hodis et al., 2001), using a standardized protocol across study sites (Kaplan et al., 2008). Quality control and reliability of the carotid artery ultrasound measurement was performed among a subset of WIHS and MACS participants and was found to have high intraclass correlations (ICC) in both WIHS (variation coefficient = 1.8%; ICC = 0.98) and MACS (variation coefficient = 1.0%; ICC=0.99; Kaplan et al., 2008).

Main outcome measure

Carotid intima media thickness at the far right CCA (CCA-IMT) was measured up to 4 times in WIHS and up to 3 times in MACS from 2004-2013. The CCA-IMT was assessed using the B-mode carotid artery ultrasounds by automated computerized edge detection of the images. The outcome of interest was change in CCA-IMT from the baseline to the follow-up assessments.

Independent variable

Past 10-year alcohol consumption was self-reported by asking about the average frequency (number of days per week) and quantity (number of drinks per drinking day) of use. The average number of drinks per week was calculated by multiplying the frequency by the quantity. We capped the maximum number of drinks per week to 14 for women and 21 for men in accordance with the definition of hazardous alcohol use (Reid et al., 1999). For example, women that reported > 14 drinks per week were given a value of 14. Current alcohol consumption was calculated by multiplying the frequency by the quantity to yield the average number of drinks per week at baseline and all follow-up assessments. Current alcohol consumption was categorized as abstinent (<1 per week), moderate (≤7 drinks per week for women or ≤14 drinks per week for men), and heavy (>7 drinks per week for women or >14 drinks per week for men).

Covariates

Covariates of interest were chosen based on our conceptual model of confounding factors in the association between alcohol consumption and early atherosclerosis development (Figure 5-1). Age was assessed in years, using participants' self-reported date of birth. Race was self-reported and categorized as white, black, and Asian/Pacific Islander or Native American/Alaskan. Self-reported smoking was assessed in number of packs smoked using standardized categories: less than half a pack per day; at least half a pack but less than one pack per day; at least one but less than two packs per day; two or more packs per day. Cumulative pack-years were calculated to determine the average pack, multiplied by 0.5, and summed across the years up to the baseline and follow-up assessments. Self-reported illicit drug use was dichotomous and measured by asking if participants used any of the following: crack or any form of cocaine; uppers (including crystal, methamphetamines, speed, ice); heroin or other opiates. Depressive symptoms were assessed at each semi-annual visit with the Center for Epidemiology Studies Depression Scale (CES-D, Radloff, 1977). Some research has found that utilizing the score of 16 or greater may inflate the rate of depression among PLWH, due to the overlapping somatic symptoms that may be present due to HIV-infection (Kalichman et al., 2000). Therefore, a score of 23 or greater was considered probable depression. Plasma HIV RNA viral load was measured using standard laboratory techniques. HIV RNA viral load was categorized as <200 copies/mL) or ≥ 200 copies/mL. Cardiovascular-related comorbidities included body mass index (BMI), hypertension (blood pressure ≥ 140/90 or if the participant had been told by a doctor that they have hypertension) and diabetes (dichotomized as having been diagnosed with diabetes versus no history of diabetes).

Data Analyses

Group-based trajectory models

To describe patterns of alcohol consumption over time, we conducted group-based trajectory models (GBTM). In the first modeling step, we assessed linear patterns of 3-5 groups, as suggested by previous research (Marshall et al., 2015a; Marshall et al., 2015b; Cook et al., 2013). Goodness-of-fit was assessed at each step using the Akaike information criteria and Bayesian information criteria (smaller the values, better the model), group posterior probabilities (PP≥0.7 is indicative of sufficient internal reliability), and mean model entropy (≥0.7 is optimal; summed PP/number of groups). The PP estimate is the probability that any one group-based trajectory adequately captures the individual patterns. Therefore, an individual pattern was assigned into the group pattern with the highest probability of group membership. Models with PP and/or model entropy values <0.7 were rejected (Andruff et al., 2009). The 95% confidence intervals (CI) of the resulting patterns were used to qualitatively assess the stability of the trajectories. Models with small CIs of trajectories were favored over wide CIs. For both cohorts, a group-based trajectory model was conducted to describe 10-year drinking patterns prior to the baseline carotid artery ultrasound assessment. Current alcohol consumption was measured and included in the models at the time of baseline and follow-up assessments (Figure 5-2). All time-varying covariates were measured at the time of baseline and follow-up assessments.

Generalized estimating equations

Crude and adjusted associations between past and current alcohol consumption patterns and the change outcome of CCA-IMT were conducted using generalized estimating equations, stratified by gender. We developed the models in a stepwise fashion by 1) assessing the effect of time on CCA-IMT, 2) assessing time, past alcohol consumption, and current alcohol consumption, 3) adjusting for aforementioned covariates, and 4) including interactions between

past alcohol consumption and time and current alcohol consumption and time. Past and current alcohol consumption patterns were considered statistically significantly associated with change in CCA-IMT at the p-value <.05 level.

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Sample characteristics by cohort are presented in Table 5-1. Mean age (years) at baseline was about 45 in women (n=1181) and 70 in men (n=395). Women were more likely to be of black race than men (60% vs. 30%). Men were more likely to report illicit drugs use (20% vs. 8%) and had higher cumulative pack-years (3.2 vs. 2.0) than women. Probable depression (24% vs. 13%) and body mass index was higher among women (28.3 vs. 25.5), while hypertension (52% vs. 20%) and diabetes (33% vs. 22%) was more likely in men than women. At baseline, men were more likely to have suppressed viral load (65% vs. 51%) compared to women. A four-group trajectory model emerged as the best fitting model for women (Figure 5-3, Panel A; model entropy 0.88) and men (Figure 5-3, Panel B; model entropy 0.92). Alcohol consumption patterns included "Abstinent" (WIHS 36%; MACS 15%, <1 drink/week throughout 10-years), "Low" (WIHS 30%; MACS 59%, low to moderate [1-2 (3) drinks/week for women (men)] throughout 10-years), "Moderate" (WIHS 28%; MACS 18% [3-4 (6-8) drinks/week for women (men)] and "Heavy" (WIHS 6%; MACS 8% heavy [> 7 (14) drinks/week for women (men)] consumption throughout 10-years). Current alcohol consumption at baseline was comparable by cohort (Abstinence: WIHS 55%, MACS 59%; Moderate WIHS 37%, MACS 36%; Heavy: WIHS 8%, MACS 5%). The mean CCA-IMT (μm) in WIHS at baseline was 731.2 (standard deviation [SD] 116.9), 734.8 (SD 115.1) at follow-up 1, 733.2 (SD 115.8) at follow-up 2, and 750.3 (SD 124.1) at follow-up 3. The mean CCA-IMT (μm) in MACS at baseline was 742.4 (SD 124.7), 756.4 (SD 124.9) at follow-up 1, and 791.7 (SD 126.4) at follow-up 2.

Crude Associations between Alcohol Consumption and CCA-IMT

Mean CCA-IMT by past and current alcohol consumption patterns and crude estimates of alcohol consumption patterns on CCA-IMT are presented in Table 5-2. Among women, baseline CCA-IMT was highest among those with past heavy (mean 752.6, 95% CI 732.4-772.9) and current heavy (mean 749.4, 95% CI 739.3-759.5) alcohol consumption. Compared to abstinence. past low (β -5.7, 95% CI -17.6-6.2, p=.35), moderate (β -9.4, 95% CI -20.3-1.5, p=.09), and heavy (β 9.2, 95% CI -12.6-31.1, p=.41) consumption was not statistically significantly associated with CCA-IMT. While there was no statistical significant crude association between current moderate consumption (β 1.3, 95% CI -3.4-6.0, p=.56) and CCA-IMT, heavy consumption was associated with increase CCA-IMT (β 11.0, 95% CI 2.1-19.8, p=.01).

The baseline CCA-IMT was highest in men with past moderate (mean 779.8, 95% CI 744.2-815.6) and current moderate (mean 759.7, 95% CI 746.6-772.7) alcohol consumption. Compared to abstinence, there were no statistically significant crude associations between past (Low: β -11.6, 95% CI -41.3-18.1, p=.44; Moderate: β 18.5, 95% CI -25.5-62.6, p=.41; Heavy: β 14.7, 95% CI -38.7-68.2, p=.59) or current (Moderate: β 0.4, 95% CI -8.0-8.7, p=.94; Heavy: β -8.9, 95% CI -26.5-8.5, p=.32) alcohol consumption patterns and CCA-IMT.

Adjusted Associations between Alcohol Consumption and CCA-IMT

Adjusted associations between past and current alcohol consumption patterns are shown in Table 5-3. Among women, most past alcohol consumption patterns were not statistically significantly associated with CCA-IMT, compared to abstinence (Low: β -6.8, 95% CI -20.4-6.8, p=.33; Heavy: β -20.2, 95% CI -46.1-5.7, p=.13). Past moderate consumption was associated with decreased CCA-IMT level (β -13.2, 95% CI -26.4-0.3, p=.05). While current moderate consumption was not statistically significantly associated with CCA_IMT (β 2.6, 95% CI -6.4-

11.7, p=.57), current heavy consumption was associated with increased CCA-IMT level (β 21.8, 95% CI 6.4-37.2, p=.01).

Among men, past alcohol consumption patterns were not statistically significantly associated with CCA-IMT (Low: β 2.7, 95% CI -29.9-35.3, p=.87; Moderate: β 24.9, 95% CI -28.6-78.3, p=.36; Heavy: β -7.6, 95% CI -72.5-57.3, p=.82). While current moderate consumption was not statistically significantly associated with CCA-IMT, compared to abstinence (β 2.0, 95% CI -23.5-27.5, p=.88), current heavy consumption was associated with a clinically significant increase in CCA-IMT level (β 33.5, 95% CI –3.4-70.4, p=.07).

Interaction terms between past alcohol consumption and time and current alcohol consumption and time were statistically significant in men (Figure 5-4), but not in women (Figure 5-5). Men in the 10-year abstinent alcohol consumption group tended to decrease in CCA-IMT level over time and had the greatest decrease in CCA-IMT by the end of follow-up (Time: β -15.9, 95% CI -26.2, -5.7, p<.01). All other 10-year consumption groups increased in CCA-IMT level over time (Time*Low β 12.5, 95% CI 4.8, 20.2, p<.01; Time*Moderate: β 14.9, 95% CI -1.0, 30.8, p=.07; Time*Heavy: β 20.1, 95% CI 1.6, 38.7, p=.03).

Discussion

We aimed to assess the association between past (10-year) and current (6-month) patterns of alcohol consumption and CCA-IMT, measured by B-mode carotid artery ultrasound. Specifically, we aimed to test the effect of heavy and moderate alcohol consumption on early atherosclerosis development among PLWH. While those in the 10-year heavy alcohol use group tended to have the highest CCA-IMT, membership in this group was not statistically significantly associated increased CCA-IMT in men and women, compared to the 10-year abstinent group.

Men and women seemed to have contradictory results regarding the effect of 10-year moderate alcohol use, with moderate drinking women having lower CCA-IMT, whereas low and moderate drinking men had higher CCA-IMT. Other studies have found inconsistent findings of alcohol effects on subclinical atherosclerosis between women and men (Zyriax et al., 2010; Lee et al., 2009; Schminke et al., 2005). These differences may be a result of the gender differences in risk factors and clinical presentation of CVD. For example, CVD in women is more likely to present as microvascular coronary disease, rather than plaque development and narrowing of the large coronary arteries (Vaccarino and Bremner, 2016). Therefore, it is possible that moderate and heavy drinking are associated with early progression of CVD, but in the small arteries and vessels of the coronary arteries.

Current heavy alcohol use was associated with statistically significant increase in CCA-IMT in women, and clinically relevant increases in men. This finding is consistent with research in HIV-uninfected populations that found heavy alcohol use to significantly increase CCA-IMT (Zyriax et al., 2010) and carotid artery stiffness (Hougaku et al., 2005).

Longitudinal effects of past and current alcohol consumption were found in men, but not women. Men in the past abstinent alcohol consumption group tended to decrease in CCA-IMT over time and had the greatest decrease in CCA-IMT by the end of follow-up, while all other 10-year consumption groups increased in CCA-IMT over time. Therefore, we did not find any level of long-term alcohol use to be beneficial to cardiovascular health in men, but rather the opposite. Interestingly, current heavy alcohol consumption was associated with a significant decrease in CCA-IMT over time. This is likely due to the fact that current heavy users had the highest baseline CCA-IMT, leaving greater opportunity to decrease over time than any other group. After adding the time and alcohol use interactions, a protective association of past moderate

alcohol consumption on CCA-IMT baseline level remained in women and current heavy use was associated with higher baseline levels of CCA-IMT in women and men. These findings are consistent with a J-curved association found in the literature (Xie et al., 2012; Kohsaka et al., 2011; Hougaku et al., 2005).

Limitations

The readers should consider some limitations of the current study. First, alcohol consumption quantity and frequency were assessed via self-report and is subject to recall and social desirability biases. These potential biases likely result in underestimation of alcohol consumption. However, this method has been established as a reliable and valid approach to alcohol use assessment (Del Boca and Darkes, 2003). Second, because we used carotid artery ultrasound to measure non-plaque CCA-IMT, these results can only be generalized to the early developmental stages of atherosclerosis in the carotid artery. Research has found CCA-IMT to be highly correlated to subclinical disease in other vascular territories when compared to other methods that detect low to no disease (Davis et al., 1999; Lester et al., 2009). Third, there are significant demographic differences between the WIHS and MACS cohorts, making direct comparisons of stratified analyses difficult. Because of these differences, we carefully controlled for confounding variables related to socio-demographic status and cardiovascular risk. Fourth, GBTM is a semi-parametric and probabilistic model that estimates grouped trajectories of the most similar individual patterns. Therefore, each trajectory group does not fully describe the individual-level patterns contained within them and should not be considered absolute.

Conclusions

In summary, the current study adds to the literature on the effect of longitudinal and current alcohol consumption on the early development of subclinical atherosclerosis among PLWH, by focusing on changes in non-plaque CCA-IMT. This study provides important

information regarding the specific effect of long-term and short-term moderate and heavy alcohol use among PLWH, and thus helps fill the gap in this area of alcohol research. It is possible that alcohol consumption has harmful effects in some person, but not others, Therefore, future research should continue to investigate the effect of alcohol use on the early development of atherosclerosis and interactions with other significant factors, such as mental health issues, social support, and antiretroviral treatments. Further research could also focus on the risk mechanism to validate the protective affect of moderate consumption by assessing the effect of alcohol consumption at different levels on pro- and anti-inflammatory and cardiac biomarkers.

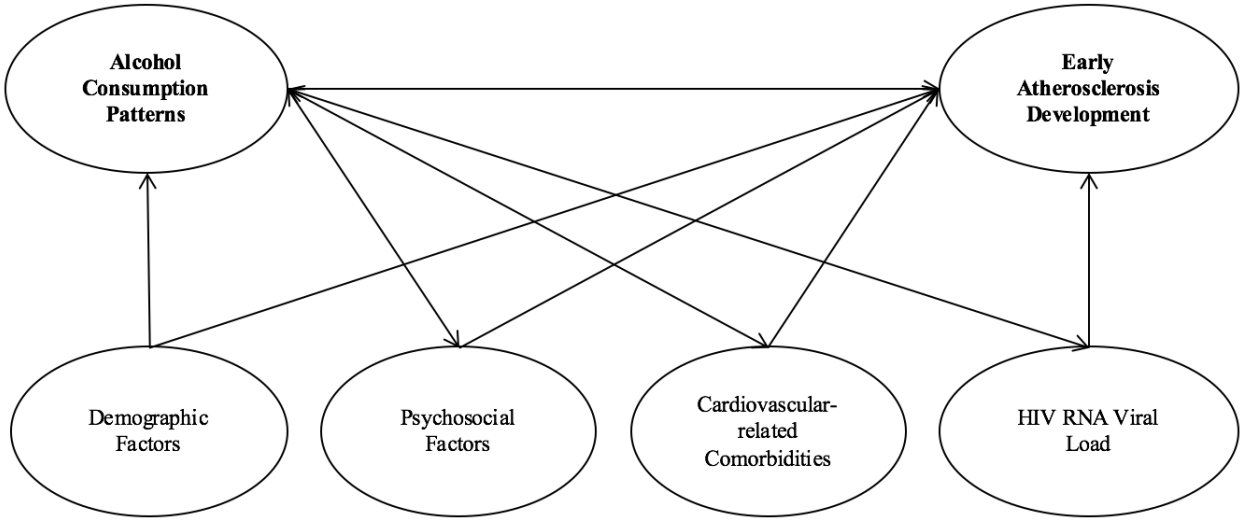

Figure 5-1. Confounding factors associated with the association between alcohol consumption and early atherosclerosis development.

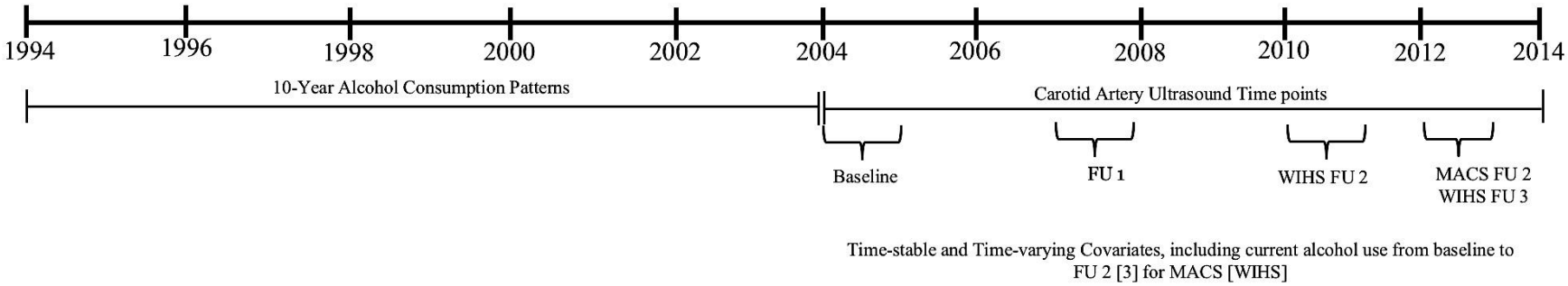

Figure 5-2. Timeline for 10-year trajectory models prior to baseline carotid artery ultrasound

Table 5-1. Baseline characteristics of persons living with HIV by cohort

Baseline Characteristics	WIHS	MACS
	N (Column %) *Mean (Standard Deviation)*	
CCA-IMT μm		
Baseline (WIHS N=1181; MACS N=395)	*731.2 (116.9)*	*742.4 (124.7)*
Follow-up 1 (WIHS N=671; MACS N=329)	*734.8 (115.1)*	*756.4 (124.9)*
Follow-up 2 (WIHS N=499; MACS N=237)	*733.2 (115.8)*	*791.7 (126.4)*
Follow-up 3 (WIHS N=542)	*750.3 (124.1)*	N/A
Race		
White	256 (22)	252 (64)
African American/Black	713 (60)	120 (30)
Other	212 (18)	23 (6)
Age (continuous), mean (SD)	*45.0 (7.6)*	*69.7 (5.6)*
Probable depression		
No	902 (76)	345 (87)
Yes	279 (24)	50 (13)
Pack-years (continuous), mean (SD)	*2.0 (2.9)*	*3.2 (6.7)*
Illicit drug use		
No	086 (92)	316 (80)
Yes	95 (8)	79 (20)
Ever diagnosed with diabetes		
No	921 (78)	263 (67)
Yes	260 (22)	132 (33)
Hypertension		
No	947 (80)	190 (48)
Yes	234 (20)	205 (52)
Body mass index, mean (SD)	*28.3 (7.3)*	*25.5 (3.7)*
HIV RNA Viral Load		
< 200 copies/Ml	599 (51)	258 (65)
≥ 200 copies/Ml	582 (49)	137 (35)
10-year alcohol consumption pattern		
Abstinence	420 (36)	59 (15)
Low	351 (30)	235 (59)
Moderate	334 (28)	71 (18)
Heavy	76 (6)	30 (8)
Current alcohol consumption		
Abstinence	651 (55)	234 (59)
Moderate	441 (37)	142 (36)
Heavy	89 (8)	19 (5)

Abbreviations: WIHS, Women's Interagency HIV Study; MACS, Multicenter AIDS Cohort Study

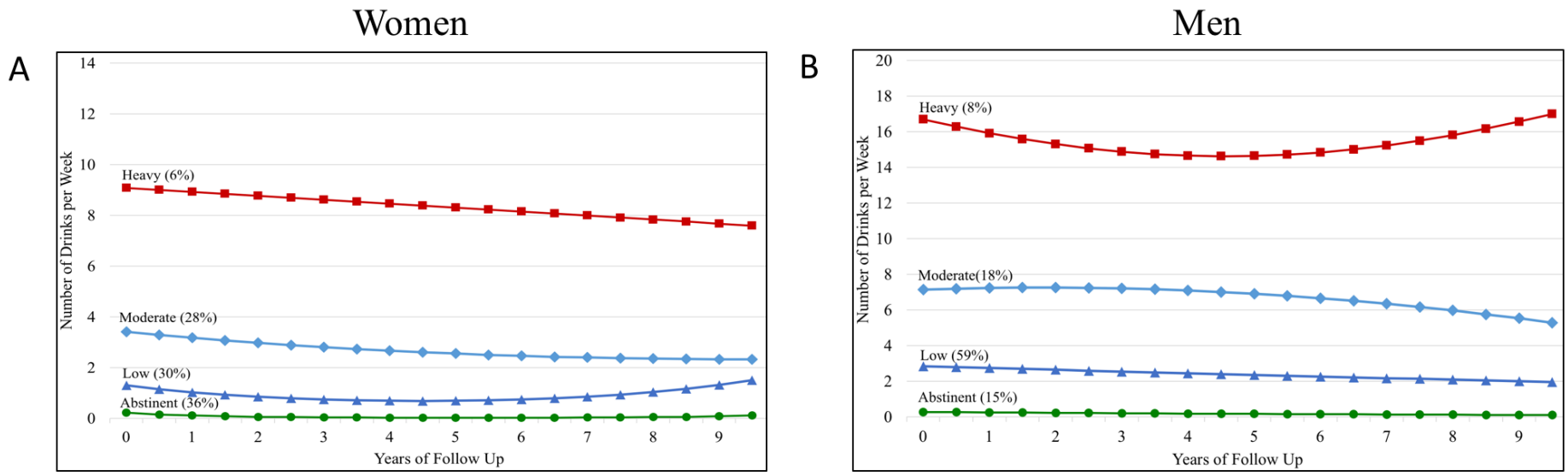

Figure 5-3. 10-year alcohol consumption trajectories by cohort. Panel A: Alcohol consumption patterns in women prior to baseline carotid artery ultrasound measurement; Panel B: Alcohol consumption patterns in men prior to baseline carotid artery ultrasound measurement

Table 5-2. Crude associations between 10-year alcohol consumption patterns, current alcohol consumption, and carotid artery intima-media thickness, by cohort

	Women's Interagency HIV Study		Multicenter AIDS Cohort Study	
	CCA-IMT, μm Mean (SD)	β (95% CI), μm	CCA-IMT, μm Mean (SD)	β (95% CI), μm
10-year Alcohol Consumption Patterns				
Abstinence	743.4 (733.9-752.9)	REF	761.3 (735.6-787.1)	REF
Low	737.7 (727.4-747.9)	-5.7 (-17.6-6.2)	749.7 (735.0-764.5)	-11.6 (-41.3-18.1)
Moderate	734.0 (724.2-743.8)	-9.4 (-20.3-1.5)	779.8 (744.2-815.6)	18.5 (-25.5-62.6)
Heavy	752.6 (732.4-772.9)	9.2 (-12.6-31.1)	776.0 (729.2-822.9)	14.7 (-38.7-68.2)
Current Alcohol Consumption				
Abstinence	738.4 (731.4-745.4)	REF	759.3 (746.6-772.1)	REF
Moderate	739.7 (732.5-747.0)	1.3 (-3.4-6.0)	759.7 (746.6-772.7)	0.4 (-8.0-8.7)
Heavy	749.4 (739.3-759.5)	11.0 (2.1-19.8)**	750.4 (731.2-769.5)	-8.9 (-26.5-8.5)

All analyses controlled for time, age, race, pack-years of cigarette use, illicit drug use, probable depression, hypertension, diabetes, and body mass index, suppressed HIV RNA viral load. Gender was controlled for in the combined analysis.
† p<.10, *p<.05, **p<.01, ***p<.001

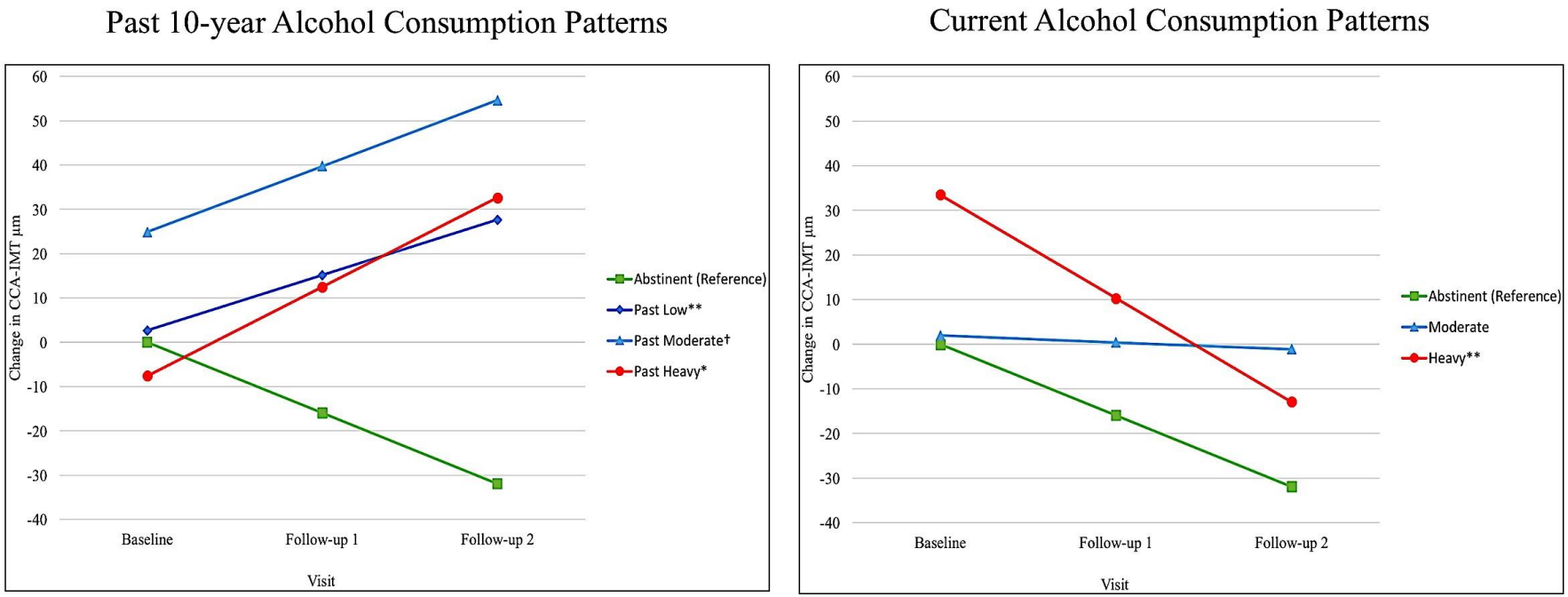

Figure 5-4. Interaction of alcohol consumption patterns and time on change in CCA-IMT µm among men.

†p < .10, *p < .05, **p < .01

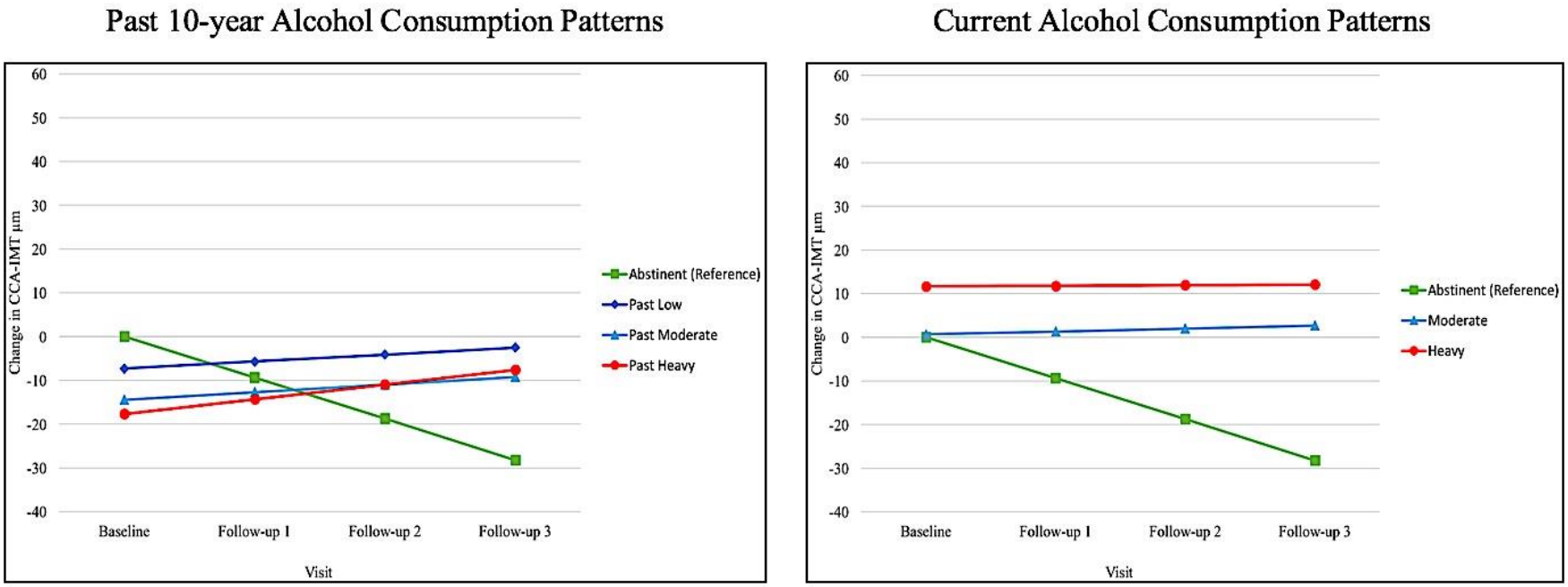

Figure 5-5. Interaction of alcohol consumption patterns and time on change in CCA-IMT µm among women

Table 5-3. Association between 10-year alcohol consumption patterns, current alcohol consumption, and carotid artery intima-media thickness, controlling for the time and alcohol use interactions, by cohort

	Women's Interagency HIV Study	Multicenter AIDS Cohort Study
	β (95% CI), μm	β (95% CI), μm
10-year Alcohol Consumption Patterns		
Abstinence	REF	REF
Low	-6.8 (-20.4-6.8)	2.7 (-29.9-35.3)
Moderate	-13.2 (-26.4-0.3)*	24.9 (-28.6-78.3)
Heavy	-20.2 (-46.1-5.7)	-7.6 (-72.5-57.3)
Current Alcohol Consumption		
Abstinence	REF	REF
Moderate	2.6 (-6.4-11.7)	2.0 (-23.5-27.5)
Heavy	21.8 (6.4-37.2)**	33.5 (-3.4-70.4)†

All analyses controlled for time, age, race, pack-years of cigarette use, illicit drug use, probable depression, hypertension, diabetes, and body mass index, suppressed HIV RNA viral load.
† p<.10, *p<.05, **p<.01, ***p<.001

CHAPTER 6
CONCLUSIONS

Accomplishments of the Dissertation

This dissertation sought to advance scientific knowledge of the associated factors of long-term heavy and moderate alcohol consumption and to fill the gap in knowledge of the effect of long-term moderate and heavy alcohol consumption on the development of atherosclerosis. Specifically, we aimed to challenge or confirm the general assumption that moderate alcohol consumption is protective to cardiovascular health, and provided evidence that addresses this relationship among PLWH. We characterized patterns of alcohol consumption among PLWH from 2004-2013 by gender and assessed the association between time-stable and –varying clinical factors of long-term heavy and moderate alcohol consumption. We also described the association between 10-year patterns of alcohol use and the prevalence and incidence of subclinical atherosclerosis, measured by B-mode carotid artery ultrasound imaging. Lastly, we assessed the longitudinal association between past 10-year and current patterns of alcohol use and carotid IMT progression.

Taken together, this research addressed an important gap in the literature regarding the possible J-curve association between alcohol consumption and cardiovascular health among PLWH, that has been found in the general population. The results of this study have implications for clinical practice and identification of PLWH with high CVD risk outside of the traditional risk framework. This research also underlines the need for consistent recommendations of alcohol consumption related to CVD risk and has the potential to highlight the importance of tailored interventions that can better address alcohol use issues that are specific to PLWH.

We expected the first objective to provide new knowledge describing alcohol consumption trajectories over time and longitudinal associations between clinical factors and

moderate and heavy alcohol consumption, among PLWH. While several alcohol patterns characterized a stable level of consumption (i.e., low/abstinence, moderate, heavy), some patterns also featured shifts in drinking overtime. This indicates that alcohol consumption should be measured longitudinally to accurately depict exposure. Results also suggested that there are significant longitudinal clinical associations of moderate and heavy consumption that may help distinguish individuals for prevention and/or early intervention. The most significant associated factors of moderate and heavy alcohol consumption, across both men and women, was longitudinal illicit drug use. The Framingham risk score was associated with increased odds for moderate and heavy alcohol consumption among women. Also among women, sub-optimal ART adherence was associated with increased odds for moderate alcohol consumption. Furthermore, having a HIV RNA viral load of 200 or greater was associated with increased odds for moderate and heavy consumption in women.

In our second objective, we expected to identify longitudinal drinking patterns that were significantly associated with prevalent and incident subclinical atherosclerosis. A particular advantage to this study was the ability to identify those who did not have subclinical atherosclerosis at baseline that later developed this outcome, years later. With this information, we were able to identify 10-year alcohol consumption patterns prior to disease development. Contrary to our hypothesis, we found that heavy alcohol consumption was not statistically significantly associated with increased risk for prevalent or incident subclinical atherosclerosis in women or men compared to abstinence. Moderate consumption was associated with 29% lower odds of prevalent disease in women and 47% lower odds of incident disease in men. While moderate alcohol consumption was not statistically significantly associated with subclinical

atherosclerosis, it is considered clinically significant and is consistent with a protective effect found in other studies.

In our third objective, we highlight the relationship between past (10-year) and current (6-month) alcohol consumption patterns and progression in non-plaque CCA-IMT among PLWH. With up to 4 repeated measurements of CCA-IMT, we were able to test the association between past and current alcohol use patterns and baseline CCA-IMT, as well as assess the longitudinal effect of these drinking patterns on change in CCA-IMT over time. In this analysis, we found that while past moderate alcohol consumption was moderately associated with a protective effect on CCA-IMT in women, no level of alcohol use was found to be protective in men. Interactions between past and current alcohol consumption and time were statistically significant in men, but not in women. Compared to abstinence, men in all other 10-year consumption groups increased in CCA-IMT over time. After adding the interactions, a protective tendency of 10-year moderate use on baseline CCA-IMT level remained in women and current heavy use was associated with higher CCA-IMT in women and men.

Public Health Recommendations and Future Directions

The U.S. Preventive Services Task Force recommends that clinicians assess all adults aged 18 years and older for alcohol misuse, and to provide support to reduce risky alcohol consumption (US Preventive Services Task Force, 2013). Further, several screening and brief intervention tools have been developed specifically for clinical use in the general and specific clinical populations (Saitz et al., 2016). In line with these recommendations, clinicians should consider screening all patients for alcohol consumption, particularly if patients report current and past illicit drug use, suboptimal ART adherence, and if patients have detectable viral load. Clinicians could also consider assessing moderate alcohol consumption, as this study found

detrimental associations of moderate use on adherence and viral load, particularly among women.

Future research should continue to investigate the effect of alcohol use on atherosclerosis and interactions with other significant factors, such as mental health issues, social support, and antiretroviral treatments. We particularly need more research conducted that confirms the protective effect of moderate alcohol use on CVD and all cause mortality among PLWH, as it is not clear whether PLWH should consume alcohol in moderation to reduce cardiovascular risk. Lastly, special attention should be paid to the effect of 'sick-quitters', or those who quit drinking due to declining health. Often times, this group features high risk for poor outcomes due to past heavy drinking, while currently being in the non-use group, skewing results toward the null. Therefore, future research should focus on characterizing those in the sick-quitter group and making efforts to separate this sub-population from the abstinent or low alcohol use group.

Advantages and Challenges of the Current Research

Utilizing the MACS and WIHS datasets to complete the objectives of the current dissertation come with many advantages and some challenges. The MACS and WIHS cohorts are incredibly rich sources of clinical, psychological, and behavioral information from those living with HIV and those at high risk for future HIV acquisition. The amount of information available for this dissertation really allowed us to explore several areas of potential cofounding factors in the relationship between alcohol consumption and subclinical atherosclerosis. Further, because these cohorts are long standing and collect data on a semi-annual basis, we had the unique opportunity to assess trends in alcohol use over time, and use these patterns to more accurately understand the risk or benefits of specific long-term alcohol use patterns on cardiovascular health. An additional advantage of these two cohorts is that many of the data

collection methods used are the same or similar in terms of using standardized questionnaires when available (i.e., using the CES-D to assess depressive mood).

Some challenges did arise, however, when using both cohorts for this dissertation research. Of note, the cohorts are of two different populations (women and men who have sex with men), with disparate recruitment methods. While neither cohort can be considered nationally representative of PLWH in general, each wave of enrollment for both cohorts had specific goals in mind that did not coincide. For example, the WIHS has been specific in recruiting women who are racially/ethnically diverse, of lower socioeconomic status, and of whom generally engage in high risk behaviors (i.e., substance use). Conversely, initial MACS participant recruitment was based centrally on those with HIV or at high risk during the early history of the HIV epidemic, mainly affecting white MSM of higher socioeconomic status. Later, MACS purposively over-sampled racially/ethnically diverse men for this reason. These demographic differences by cohort make gender comparisons difficult, if not sometimes impossible, as we cannot rule out the possibility that gender effects are not merely the effect of population or recruitment strategy differences. An additional challenge in using both cohorts is the fact that not all data collection methods are the same, with many questions being asked differently or laboratory tests using different cut-offs. Similarly, because these are two different cohorts and datasets, the variable names within these datasets that are describing the same indicator are also not centralize, which resulted in significant additional time for data cleaning.

APPENDIX A
ADDITIONAL CHAPTER 3 TABLES

Table A-1. Factors associated with missing data in Aim 1

	WIHS			MACS		
Characteristics	Percent Missing		P	Percent Missing		P
	<10	10+		<10	10+	
	742 (66)	381 (34)		377 (63)	220 (37)	
Race			.12			.83
White	151 (61)	97 (39)		200 (64)	111 (36)	
Black	453 (67)	223 (33)		139 (62)	86 (38)	
Other	138 (69)	61 (31)		38 (62)	23 (38)	
Income			.56			.95
< $10,000	375 (68)	176 (32)		105 (70)	45 (30)	
$10,000-$30,000	239 (70)	100 (29)		86 (68)	40 (32)	
≥ $30,000	125 (66)	64 (34)		146 (69)	65 (31)	
Probable Depression			.15			.88
No	532 (65)	313 (35)		324 (63)	190 (37)	
Yes	160 (70)	68 (30)		53 (64)	30 (36)	
Illicit Drug Use			<.01			.04
No	693 (70)	297 (30)		284 (71)	116 (29)	
Yes	44 (54)	37 (46)		68 (61)	44 (39)	
BMI Status			.001			<.001
Underweight	335 (69)	152 (31)		51 (38)	82 (62)	
Normal	125 (56)	100 (44)		165 (72)	63 (28)	
Overweight	282 (69)	129 (31)		161 (68)	75 (32)	
Diabetes			<.01			.02
No	527 (64)	299 (36)		232 (60)	156 (40)	
Yes	215 (72)	82 (28)		145 (69)	64 (31)	
CD4+ T-cell count			<.001			<.001
≥ 500 cells/mm^3	319 (72)	124 (28)		189 (72)	75 (28)	
300-500 cells/mm^3	219 (68)	104 (32)		103 (66)	54 (34)	
< 300 cells/mm^3	204 (57)	153 (43)		85 (48)	91 (52)	
Suppressed Viral load			.70			.90
No	324 (65)	171 (34)		113 (63)	67 (37)	
Yes	418 (66)	210 (33)		264 (63)	153 (37)	
Age, years	44.9 (7.4)	45.3 (7.9)	.48	57.4 (7.5)	56.2 (8.0)	.07
FRS	8.4 (6.1)	8.4 (5.9)	.99	11.3 (3.0)	10.7 (3.7)	.03
Cumulative ART use, years	13.6 (4.4)	9.3 (4.9)	<.001	10.5 (3.8)	7.7 (3.8)	<.001
Alcohol Use			.20			.25
Abstinent	569 (65)	310 (35)		237 (61)	152 (39)	
Moderate	121 (71)	49 (29)		120 (68)	56 (32)	
Heavy	52 (70)	22 (30)		20 (62)	12 (37)	

APPENDIX B
ADDITIONAL CHAPTER 4 TABLES

Table B-1. Full model estimates of covariates and prevalent subclinical atherosclerosis, by cohort

	Women's Interagency HIV Study (WIHS)				Multicenter AIDS Cohort Study (MACS)			
	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value
Race (Ref= White)								
African American/Black	0.71 (0.44-1.13)	.15	0.73 (0.42-1.23)	.23	0.38 (0.20-0.73)	.004	0.40 (0.19-0.82)	.01
Other	0.29 (0.15-0.57)	<.001	0.34 (0.17-0.68)	.002	0.40 (0.15-1.09)	.07	0.57 (0.20-1.62)	.28
Age	1.09 (1.06-1.12)	<.001	1.09 (1.06-1.12)	<.001	0.99 (0.96-1.03)	.72	1.01 (0.98-1.05)	.28
Pack-years	1.10 (1.04-1.16)	<.001	1.08 (1.02-1.15)	.009	1.07 (1.04-1.11)	<.001	1.07 (1.03-1.11)	<.001
Illicit drug use (Ref = No)	2.52 (1.46-4.38)	<.001	1.83 (0.99-3.38)	.05	0.73 (0.38-1.39)	.34	0.60 (0.29-1.25)	.17
BMI status	0.95 (0.92-0.98)	<.001	0.97 (0.94-1.00)	.06	0.94 (0.88-1.00)	.06	0.93 (0.87-1.00)	.05
Diabetes (Ref = No)	1.47 (0.97-2.22)	.07	1.45 (0.91-2.32)	.12	1.24 (0.75-2.03)	.40	1.37 (0.78-2.40)	.27
Hypertension (Ref = No)	1.41 (0.92-2.15)	.11	0.92 (0.57-1.51)	.75	1.52 (0.94-2.46)	.09	1.60 (0.95-2.72)	.08
Hepatitis C-Co Infection (Ref = No)	2.03 (1.36-3.02)	<.001	1.37 (0.88-2.13)	.16	1.99 (1.03-3.86)	.04	1.69 (0.81-3.52)	.16
Viral Load ≥ 200 copies/mL (Ref = < 200 copies/mL)	1.32 (0.90-1.94)	.15	1.29 (0.85-1.97)	.23	0.87 (0.46-1.65)	.68	0.93 (0.46-1.89)	.85
Alcohol Consumption Patterns (Ref = Abstinence)								
Low-Moderate	0.78 (0.52-1.17)	.23	0.71 (0.45-1.10)	.12	0.99 (0.51-1.93)	.98	1.08 (0.51-2.28)	.84
Heavy	1.39 (0.66-2.92)	.38	0.86 (0.38-1.97)	.73	1.39 (0.51-3.77)	.52	1.16 (0.38-3.54)	.79

Table B-2. Full model estimates of covariates and prevalent subclinical atherosclerosis, overall

	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value
Gender (Ref = Female)	1.88 (1.39-2.56)	<.001	0.74 (0.47-1.15)	.18
Race (Ref= White)				
African American/Black	0.71 (0.44-1.13)	.15	0.54 (0.37-0.80)	.002
Other	0.29 (0.15-0.57)	<.001	0.31 (0.18-0.55)	<.001
Age	1.09 (1.06-1.12)	<.001	1.06 (1.03-1.08)	<.001
Pack-years	1.10 (1.04-1.16)	<.001	1.07 (1.04-1.11)	<.001
Illicit drug use (Ref = No)	2.52 (1.46-4.38)	<.001	1.13 (0.71-1.79)	.60
BMI status	0.95 (0.92-0.98)	<.001	0.96 (0.93-0.99)	.005
Diabetes (Ref = No)	1.47 (0.97-2.22)	.07	1.40 (0.98-1.99)	.06
Hypertension (Ref = No)	1.41 (0.92-2.15)	.11	1.27 (0.89-1.80)	.18
Hepatitis C-Co Infection (Ref = No)	2.03 (1.36-3.02)	<.001	1.46 (1.01-2.11)	.04
Viral Load ≥ 200 copies/mL (Ref = < 200 copies/mL)	1.32 (0.90-1.94)	.15	1.30 (0.92-1.85)	.14
Alcohol Consumption Patterns (Ref = Abstinence)				
Low-Moderate	0.97 (0.69-1.35)	.84	0.78 (0.54-1.13)	.20
Heavy	1.54 (0.86-2.75)	.14	0.99 (0.52-1.88)	.97

Table B-3. Full model estimates of covariates and incident subclinical atherosclerosis, by cohort

	Women's Interagency HIV Study (WIHS)				Multicenter AIDS Cohort Study (MACS)			
	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value
Race (Ref= White)								
African American/Black	0.83 (0.43-1.61)	.58	0.59 (0.28-1.22)	.15	0.82 (0.45-1.50)	.52	0.78 (0.37-1.65)	.52
Other	0.70 (0.29-1.70)	.43	0.36 (0.17-1.21)	.11	0.61 (0.23-1.58)	.31	0.91 (0.32-2.58)	.86
Age	1.09 (1.05-1.13)	<.001	1.07 (1.03-1.12)	<.001	1.03 (0.99-1.07)	.15	1.05 (1.00-1.10)	.04
Pack-years	1.08 (1.02-1.15)	<.01	1.05 (0.98-1.13)	.14	1.10 (1.04-1.16)	<.001	1.12 (1.06-1.20)	<.001
Illicit drug use (Ref = No)	1.65 (0.65-4.16)	.29	1.12 (0.38-3.31)	.84	1.14 (0.54-2.44)	.73	1.51 (0.64-3.58)	.35
BMI status	0.92 (0.87-0.96)	<.001	0.91 (0.86-0.96)	.001	1.01 (0.95-1.07)	.77	0.99 (0.92-1.06)	.76
Diabetes (Ref = No)	1.71 (0.97-3.00)	.06	1.30 (0.69-2.43)	.41	1.27 (0.71-2.27)	.42	1.54 (0.80-2.99)	.20
Hypertension (Ref = No)	1.77 (1.02-3.07)	.04	1.53 (0.79-2.97)	.21	1.98 (1.11-3.52)	.02	1.65 (0.87-3.12)	.13
Hepatitis C-Co Infection (Ref = No)	2.42 (1.30-4.51)	<.01	1.44 (0.70-2.94)	.32	1.25 (0.60-2.60)	.55	0.79 (0.34-1.86)	.59
Viral Load ≥ 200 copies/mL (Ref = < 200 copies/mL)	1.40 (0.79-2.47)	.24	1.82 (0.95-3.47)	.07	0.40 (0.12-1.35)	.14	0.36 (0.10-1.29)	.12
Alcohol Consumption Patterns (Ref = Abstinence)								
Low-Moderate	0.95 (0.54-1.68)	.86	1.05 (0.57-1.92)	.88	0.50 (0.26-0.98)	.04	0.53 (0.25-1.13)	.10
Heavy	1.30 (0.52-3.18)	.56	1.08 (0.39-3.01)	.87	1.17 (0.43-3.18)	.75	1.40 (0.46-4.26)	.55

Table B-4. Full model estimates of covariates and incident subclinical atherosclerosis, overall

	Crude Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio[a] (95% CI)	*P* value
Gender (Ref = Female)	1.61 (1.09-2.38)	.02	0.54 (0.29-1.01)	.05
Race (Ref= White)				
African American/Black	0.73 (0.48-1.12)	.15	0.63 (0.38-1.04)	.07
Other	0.59 (0.32-1.12)	.11	0.61 (0.30-1.21)	.15
Age	1.05 (1.03-1.07)	<.001	1.06 (1.03-1.09)	<.001
Pack-years	1.09 (1.05-1.13)	<.001	1.10 (1.05-1.14)	<.001
Illicit drug use (Ref = No)	1.46 (0.81-2.61)	.20	1.11 (0.58-2.12)	.75
BMI status	0.94 (0.91-0.97)	<.001	0.94 (0.90-0.98)	<.01
Diabetes (Ref = No)	1.55 (1.04-2.32)	.03	1.40 (0.90-2.18)	.13
Hypertension (Ref = No)	1.98 (1.34-2.93)	<.001	1.66 (1.06-2.60)	.03
Hepatitis C-Co Infection (Ref = No)	1.81 (1.13-2.91)	.01	1.07 (0.63-1.83)	.80
Viral Load ≥ 200 copies/mL (Ref = < 200 copies/mL)	0.92 (0.57-1.48)	.72	1.16 (0.67-2.00)	.59
Alcohol Consumption Patterns (Ref = Abstinence)				
Low-Moderate	0.86 (0.57-1.32)	.50	0.79 (0.50-1.27)	.34
Heavy	1.45 (0.76-2.77)	.26	1.28 (0.63-2.61)	.49

Table B-5. Sample Characteristics between those with and without follow-up in Aim 2

	WIHS (n=800 minus 125 [those with Prev disease]; n=675)			MACS (n=348 minus 90 [those with Prev disease]; n=258)		
	No FU (N=387)	FU (N=288)	P-value	No FU (N = 63)	FU (N=195)	P-value
Race			.03			<.001
White	74 (19)	34 (12)		55 (87)	102 (52)	
Black	217 (56)	172 (60)		6 (10)	68 (35)	
Other (Asian, Native American, etc)	96 (25)	82 (28)		2 (3)	25 (13)	
Age, mean (95% CI)	45.3 (44.6-46.1)	44.5 (43.7-45.4)	.63	51.3 (50.1-52.4)	57.8 (56.7-59.0)	<.001
Smoking pack-years, mean (95% CI)	2.6 (2.3-2.9)	2.4 (2.0-2.7)	.32	4.1 (2.5-5.7)	2.5 (1.8-3.3)	.06
Illicit drug use			.84			.40
No	359 (93)	266 (92)		48 (76)	158 (81)	
Yes	28 (7)	22 (8)		15 (24)	37 (19)	
Body Mass Index, mean (95% CI)	28.3 (27.5-29.0)	28.8 (27.9-29.6)	.37	25.4 (24.6-26.2)	26.1 (25.4-26.7)	.18
Hypertension			.56			.69
No	295 (76)	225 (78)		38 (60)	123 (63)	
Yes	92 (24)	63 (22)		25 (40)	72 (37)	
Diabetes			.46			.39
No	297 (77)	214 (74)		45 (71)	128 (66)	
Yes	90 (23)	74 (26)		18 (29)	67 (79)	
Hepatitis C status			.82			.85
Negative	290 (75)	218 (76)		56 (89)	175 (90)	
Positive	97 (25)	70 (42)		7 (11)	20 (10)	
HIV RNA Viral Load			.60			<.001
< 200 copies/mL	203 (52)	157 (55)		39 (62)	178 (91)	
≥ 200 copies/mL	184 (48)	131 (45)		24 (38)	17 (9)	
10-year alcohol consumption pattern			.29			.24
Abstinent-Low	135 (35)	96 (33)		6 (15)	35 (18)	
Moderate	226 (58)	180 (62)		53 (27)	145 (74)	
Heavy	26 (7)	12 (4)		4 (21)	15 (79)	

APPENDIX C
ADDITIONAL CHAPTER 5 TABLES

Table C-1. Cross-tabulation of past and current alcohol consumption patterns at baseline carotid artery ultrasound

	WIHS			MACS		
	Current Alcohol Consumption			Current Alcohol Consumption		
	Abstinent	Moderate	Heavy	Abstinent	Moderate	Heavy
Past Alcohol Consumption						
Abstinent	391 (93.1)	28 (6.7)	1 (0.2)	59 (100)	0 (0)	0 (0)
Low	177 (50.4)	165 (47.0)	9 (2.6)	154 (65.5)	79 (33.6)	2 (0.85)
Moderate	75 (22.5)	223 (66.8)	36 (10.8)	17 (23.9)	52 (73.2)	2 (2.82)
Heavy	8 (10.5)	25 (32.9)	43 (56.6)	4 (13.3)	11 (36.7)	15 (50.0)

Table C-2. Crude and adjusted model estimates of covariates on carotid artery intima-thickness among women

	Crude β (95% CI),	P value	Adjusted β (95% CI), μm	P value
Time	8.43 (6.83, 10.0)	<.001	-8.23 (-10.7, -5.79)	<.001
Race (Ref= White)				
African American/Black	40.0 (23.4, 56.6)	<.001	34.2 (20.1, 48.2)	<.001
Other	-6.3 (-25.6, 13.0)	.52	-7.01 (-23.4, 9.39)	.40
Age	6.92 (6.03, 7.81)	<.001	6.51 (5.66, 7.42)	<.001
Pack-years	4.62 (2.03, 7.20)	<.001	4.46 (2.09, 6.83)	<.001
Illicit drug use (Ref = No)	4.72 (-2.83, 12.3)	.22	2.32 (-5.71, 10.3)	.57
Probable Depression (Ref = No)	3.50 (-1.65, 8.66)	.18	3.18 (-1.90, 8.26)	.22
BMI status	0.68 (-.008, 1.36)	.05	0.99 (0.30,1.68)	<.01
Diabetes (Ref = No)	37.1 (20.9, 53.2)	<.001	23.2 (9.22, 37.1)	<.001
Hypertension (Ref = No)	10.8 (5.44, 16.2)	<.001	5.71 (0.22, 11.2)	.04
Viral Load ≥ 200 copies/mL (Ref = < 200 copies/mL)	1.13 (-3.44, 5.70)	.63	1.04 (-3.55, 5.63)	.66
Past Alcohol Consumption Pattern (Ref = Abstinence)				
Low	-5.71 (-17.6, 6.18)	.35	-3.30 (-14.8, 8.16)	.57
Moderate	-9.40 (-2-.3, 1.54)	.09	-10.8 (-21.8, 0.19)	.05
Heavy	9.25 (-12.6, 31.1)	.41	-12.5 (-34.2, 9.1)	.26
Current Alcohol Consumption Pattern (Ref = Abstinence)				
Moderate	1.32 (-3.42, 6.06)	.56	2.44 (-2.49, 7.38)	.33
Heavy	11.0 (2.11, 19.8)	.01	12.2 (3.13, 21.3)	<.01

Table C-3. Crude and Adjusted model estimates of covariates on carotid artery intima-thickness among men

	Crude β (95% CI),	P value	Adjusted β (95% CI), μm	P value
Time	23.1 (19.6, 26.6)	<.001	-6.10 (-14.5, 2.26)	.15
Race (Ref= White)				
African American/Black	28.4 (1.64, 55.1)	.04	57.9 (30.7-85.0)	<.001
Other	-12.8 (-55.4, 29.7)	.55	39.1 (-3.71, 82.0)	.07
Age	6.85 (4.82, 8.89)	<.001	7.75 (5.51, 9.98)	<.001
Pack-years	2.21 (0.61, 3.80)	<.01	1.87 (0.29, 3.45)	.02
Illicit drug use (Ref = No)	3.00 (-8.03, 14.0)	.59	2.22 (-8.93, 13.4)	.70
Probable Depression (Ref = No)	6.48 (-2.61, 15.6)	.16	9.18 (-0.13, 18.5)	.05
BMI status			1.03 (-0.24, 2.31)	.11
Diabetes (Ref = No)	14.5 (-11.0, 40.1)	.26	0.06 (-23.7, 23.8)	.99
Hypertension (Ref = No)	-5.88 (-12.7, 0.91)	.09	-3.09 (-9.81, 3.64)	.37
Viral Load ≥ 200 copies/mL (Ref = < 200 copies/mL)	-3.17 (-11.5, 5.13)	.45	-3.87 (-12.4, 4.65)	.37
Past Alcohol Consumption Pattern (Ref = Abstinence)				
Low	-11.6 (-41.3, 18.1)	.44	25.2 (-3.01, 53.4)	.08
Moderate	18.5 (-25.5, 62.6)	.41	51.2 (6.91, 95.5)	.02
Heavy	14.7 (-38.7, 68.2)	.59	32.3 (-21.9, 86.6)	.24
Current Alcohol Consumption Pattern (Ref = Abstinence)				
Moderate	0.40 (-8.00, 8.68)	.94	-0.31 (-9.02, 8.39)	.94
Heavy	-8.96 (-26.5, 8.55)	.32	-13.3 (-32.1, 5.54)	.17

Table C-4. Full model estimates of covariates on carotid artery intima-thickness among men and women, adjusting for time by alcohol use interactions

	Women's Interagency HIV Study		Multicenter AIDS Cohort Study	
	Adjusted β (95% CI),	P value	Adjusted β (95% CI), μm	P value
Time	-9.11 (-12.4, -5.79)	<.001	-15.9 (-26.2, -5.68)	<.01
Race (Ref= White)				
African American/Black	34.1 (20.1, 48.2)	<.001	56.4 (29.2, 83.6)	<.001
Other	-6.91 (-23.3, 9.50)	.41	39.0 (-3.6, 81.6)	.07
Age	6.54 (5.67, 7.42)	<.001	7.78 (5.56, 9.99)	<.001
Pack-years	4.46 (1.99, 6.94)	<.001	1.76 (0.19, 3.33)	.03
Illicit drug use (Ref = No)	2.15 (-5.92, 10.2)	.60	3.83 (-7.46, 15.1)	.51
Probable Depression (Ref = No)	2.96 (-2.10, 8.01)	.25	9.42 (-1.01, 19.8)	.08
BMI status	0.98 (0.35, 0.29)	<.01	0.97 (-0.33, 2.27)	.14
Diabetes (Ref = No)	23.2 (9.24, 37.1)	<.001	-0.21 (-23.9, 23.5)	.99
Hypertension (Ref = No)	5.76 (0.22, 11.3)	.04	-4.27 (-11.0, 2.49)	.21
Viral Load ≥ 200 copies/mL (Ref = < 200 copies/mL)	1.10 (-3.53, 5.72)	.64	-2.85 (-11.2, 5.47)	.50
Past Alcohol Consumption Pattern (Ref = Abstinence)				
Low	-6.80 (-20.4, 6.78)	.33	2.67 (-29.9, 35.3)	.87
Moderate	-13.2 (-26.4, -.03)	.05	24.9 (-28.6, 78.3)	.36
Heavy	-20.2 (-46.1, 5.72)	.13	-7.60 (-72.5, 57.3)	.82
Current Alcohol Consumption Pattern (Ref = Abstinence)				
Moderate	2.63 (-6.40, 11.7)	.57	1.98 (-23.5, 27.5)	.88
Heavy	21.8 (6.40, 37.2)	<.01	33.5 (-3.43, 70.4)	.07
Past Alcohol Consumption Pattern X Time				
Low	1.85 (-2.46, 6.17)	.40	12.5 (4.77, 20.2)	<.01
Moderate	1.23 (-3.18, 5.63)	.58	14.9 (-1.02, 30.8)	.07
Heavy	3.61 (-4.01, 11.2)	.35	20.1 (1.57, 38.7)	.03
Current Alcohol Consumption Pattern X Time				
Moderate	0.03 (-3.68, 3.75)	.98	-1.55 (-14.3, 11.2)	.81
Heavy	-4.06 (-11.1, 3.01)	.26	-23.2 (-41.1, -5.36)	.01

Table C-5. Sample Characteristics between those with and without follow-up in Aim 3

	WIHS			MACS		
Baseline Characteristics	No FU 485 (41)	FU 696 (59)	p-value	No FU 51 (13)	FU 344 (87)	p-value
Race			.15			.53
White	116 (24)	140 (20)		36 (70)	216 (63)	
Black	277 (57)	436 (63)		13 (25)	107 (31)	
Other	92 (19)	120 (17)		2 (9)	21 (6)	
Probable Depression			.04			.81
No	356 (73)	546 (78)		44 (86)	301 (88)	
Yes	129 (27)	150 (22)		7 (14)	43 (12)	
Illicit Drug Use			.13			.65
No	439 (91)	647 (93)		42 (82)	274 (80)	
Yes	46 (9)	49 (7)		9 (18)	70 (20)	
Diabetes			.69			.74
No	381 (79)	540 (78)		35 (69)	228 (66)	
Yes	104 (21)	156 (22)		16 (31)	116 (34)	
Suppressed Viral load			.48			.17
No	233 (48)	349 (50)		22 (43)	115 (33)	
Yes	252 (52)	347 (50)		29 (57)	229 (67)	
Age, years	45.4 (8.1)	44.8 (7.2)	.17	69.1 (5.5)	69.8 (5.6)	.44
BMI Status	27.6	28.8	<.01	25.6 (4.3)	25.5 (3.7)	.76
Pack-years	2.2 (3.1)	1.8 (2.8)	.03	2.2 (5.1)	3.3 (6.9)	.17
Past Alcohol Use			.84			.58
Abstinent	177 (36)	243 (35)		6 (12)	53 (15)	
Low	144 (30)	207 (30)		32 (63)	203 (59)	
Moderate	131 (27)	203 (29)		11 (22)	60 (17)	
Heavy	33 (7)	43 (57)		2 (4)	28 (8)	
Current Alcohol Use			.84			.44
Abstinent	268 (55)	383 (55)		26 (51)	208 (60)	
Moderate	183 (38)	258 (37)		22 (43)	120 (35)	
Heavy	34 (7)	55 (8)		3 (6)	16 (5)	
Intima-Medial Thickness	740.7 (118.1)	724.7 (115.7)	0.02	741.1 (123.4)	742.6 (125.1)	.93

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BIOGRAPHICAL SKETCH

Natalie Chichetto graduated suma cum laude from the University of Missouri in St. Louis with a Bachelor of Art degree in Psychology and Trauma Studies in 2009 and received her Master of Social Work degree from Washington University in St. Louis with a focus in Mental Health and Research Specialization in 2011. She entered the PhD program in Epidemiology at the University of Florida in 2012. During her time as a PhD student, she was awarded the Graduate School Fellowship, which provided up to 4 years of full funding. In 2015, Natalie was awarded an F31 Individual Research Fellowship (F31 AA024064) through the National Institute for Alcohol Abuse and Alcoholism to fund the last two years of her studies and dissertation work. Her research interests are in behavioral cardiology and chronic disease prevention among vulnerable populations, as well as capacity building at the policy, health care, and community levels to effectively treat and reduce chronic diseases.