THE RELATIONSHIP BETWEEN ALCOHOL USE, MENTAL HEALTH SYMPTOMS, AND RETENTION IN CARE IN WOMEN LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS

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Abstract

At-risk drinking is defined as drinking above the recommended limits, which is no more than four drinks (one drink contains 14 grams of pure alcohol) in one day for men (three for women) and no more than 14 drinks in one week for men (seven for women). At-risk drinking is associated with adverse health outcomes in the general population. For persons with HIV (PHIV), they may have increased risk for developing adverse outcomes even at lower levels of consumption such as increased risk of liver damage, more rapid virus growth, increased risk of depression, decreased medication adherence, and increased engagement in high risk sexual behaviors, resulting in the possibility of reinfection with HIV or other sexually transmitted infections (STIs). What's worse, the use of alcohol in PHIV is a concern not only for younger adults but also for those in older cohorts. However, there are lack of studies on how alcohol use affects health outcomes exclusively targeting PHIV with advanced age. This is especially concerning because with the development of antiretroviral therapy (ART), the number of aged PHIV is growing. In the first manuscript, a systematic review as conducted to evaluate existing studies on the association between alcohol use and medication adherence, engagement in high risk sex behaviors, resource utilization, HIV progression, depression, and survival in studies that included PHIV with an average age 40 and above.

Anxiety is prevalent among PHIV, especially among women with HIV (WHIV). It may have both direct and indirect effects on HIV/AIDS progression. Although the relationship between alcohol use and depression has been extensively examined, studies on alcohol use and anxiety among PHIV are limited. Thus, in the second manuscript, I examined the association between changes in generalized anxiety and changes in alcohol use among WHIV over a period of 12 months.

Engagement in health care system for clinical appointments and treatment, is one step in the HIV Care Continuum that is important for PHIV to suppress viral load and decrease mortality. Unfortunately, a significant proportion of PHIV have poor engagement in HIV care. Although there

are extensive literature demonstrating the negative relationship between mental health symptoms and medication adherence, there have not been much studies examining mental health symptoms and likelihood of attending primary care visits among PHIV, especially WHIV. Thus, in the third manuscript, I examined the impact of baseline alcohol use, anxiety, and depression on likelihood of attending primary care visits among WLHV.

Data of the second and third manuscript came from two concurrently recruited cohorts of WHIV. One was a randomized controlled trial (RCT) designed to test the effectiveness of a brief alcohol intervention (BI) among WHIV with baseline at-risk drinking (defined as 8 or more drinks/week, 2 or more binge drinking episodes [defined as 4 or more drinks/occasion] in the past six months, or TWEAK score ≥2). The TWEAK alcohol screening consists of five-questions with a total score of 7 points (the first two questions counts for 2 points each, other questions worth 1 point). A total score ≥2 indicates at-risk drinking. The second cohort was a concurrently recruited sample of WHIV without at-risk drinking at baseline from the same clinic. The parent studies were registered at clinicaltrials.gov: NCT00127231 and were approved by the Johns Hopkins Medicine Institutional Review Board.

Participants were recruited between March 2006 and September 2010 through several methods, including clinic flyers, provider referral, waiting room recruitment, and review of drinking data obtained from an audio-computer-assisted-self-interview (ACASI) routinely administered to patients who have consented to enroll in the HIV Clinical Cohort every six months. Parent studies inclusion criteria included women who 1) had a confirmed HIV infection; 2) received outpatient care at the Johns Hopkins HIV Clinic; 3) were 18 years of age or older; 4) were not receiving treatment for an alcohol use disorder (AUD); 5) not pregnant; and 6) had no history of psychosis at the time of enrollment. Women in the RCT had visits at baseline and three, six, and twelve months post-enrollment; women in the non-at-risk drinking cohort had visits at baseline, and six, and twelve months post-enrollment.

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I grew up in China and was used to develop a stereotypical opinion of the nursing field. Through my observations in Chinese hospitals, most nurses are educated at an associate or even high school level and follow physicians' orders in a non-creative and non-autonomic manner. It seems that research and policy innovations are not tangible in this profession. However, after two years of BSN study at Emory, I gained a more profound understanding of nursing research. For every practice, I observed in the clinical setting, I found research strongly connected to improving practices to yield the best patient outcome. Nursing research now more than ever urges my generation to devote our diligence, intelligence, passion, and creativity to addressing the emerging issues regarding equal

access to healthcare, chronic disease prevention and management, and the aging population. Thus, I determined to seek a nursing PhD study at my very early career.

After getting the offer from Johns Hopkins, I could not be more excited because I could never think or even dream about this offer before. I am also very grateful that the school offers fellowship that relieved financial burden for me and my family for my study. Three years' study seemed transient as I even vividly remembered the first day of school, full of curiosity and innocence. What I learned most during the past three years is that 1). *Doing research is a life-long learning process*. I should never expect to reply on existing knowledge to conquer the challenges I encounter now and in the future. I should constantly update my knowledge base and skill sets. 2). *Doing research requires us to turn frustration into motivation*. Only when we feel frustrated can we realize our limitations and make process. During the past three years, I often, if not always feel frustrated with myself and gradually learn to live with it and live with it in peace. Upon graduation, I only sense a need to further develop my research skills rather than feel accomplished. 3). *Doing research requires strong teamwork and guidance.* The great mentors I encountered really help me get into research, not only about how to choose a proper statistical method and how to write a manuscript but how to come up with a research question, how to think about an issue thoroughly, and work on it in a team. I really appreciate their efforts and patience with me. I know I am often thinking from the perspective of a new researcher. *As for a career in research, I only marched one step out of a thousand miles.*

Contents

Introduction

Alcohol Use

Alcohol use is prevalent among women with human immunodeficiency virus (WHIV). Among 1123 WHIV in the Women's Interagency HIV Study (WIHS), 62% reported current alcohol use and 7% reported heavy use (Kelso-Chichetto et al., 2017). At-risk alcohol use among women, defined as ≥4 standard drinks (one standard drink contains 14 grams of pure alcohol (National Institute on Alcohol Abuse and Alcoholism, 2016)) per occasion, or average daily drinking of >1 drink, interferes with entry and retention in the HIV care continuum (Kay, Batey, & Mugavero, 2016)-the steps that persons with HIV (PHIV) progress through in order to achieve and maintain viral suppression (Braithwaite & Bryant, 2010; Braithwaite et al., 2005; Erickson, Becker, Shaw, Kasper, & Keynan, 2015; Etienne, Hossain, Redfield, Stafford, & Amoroso, 2010; Fatch et al., 2013; Gordon et al., 2006; Kelso-Chichetto et al., 2017; S. Lee et al., 2016; Monroe et al., 2016a). These steps include linkage and retention in care, antiretroviral receipt and adherence, and viral suppression. Thus, at-risk drinking may increase the risk of developing adverse health outcomes among PHIV. This problem may be further compounded among WHIV since women are biologically more vulnerable to the effects of alcohol (Cole-Harding & Wilson, 1987; Frezza et al., 1990) and are more likely to delay alcohol treatment compared with men (Green, Freeborn, & Polen, 2001).

Anxiety

Anxiety is more prevalent among women compared with men in the general population and among WHIV compared with un-infected women (Chander & McCaul, 2003; McLean, Asnaani, Litz, & Hofmann, 2011; Saadat, Behboodi, & Saadat, 2015; van den Heuvel et al., 2013). This is associated with the fact that living with HIV can be a difficult experience and is associated with onset of comorbid mental disorders (Saadat et al., 2015). For example, HIV-related experiences such as a recent diagnosis of HIV (M.-K. Kee et al., 2015) and greater HIV-related stigma (Kamen et al., 2015) have been associated with increased symptoms of anxiety and emotional distress among PHIV. Demographic factors, drug use, and social support are also important predictors of anxiety among PHIV (Catz, Gore-Felton, & McClure, 2002; M. K. Kee et al., 2015). Anxiety may also have both direct and indirect negative effects on HIV/AIDS progression (Chander, Himelhoch, & Moore, 2006). The reported prevalence of anxiety among WHIV varies widely in the literature (from 1.91% to over 40%) (Goggin, Engelson, Rabkin, & Kotler, 1998; Morrison et al., 2002; Niu, Luo, Liu, Silenzio, & Xiao, 2016) depending on means of assessment of anxiety (Chander et al., 2006), types

of anxiety assessed, and differences in participants' characteristics such as social-demographic factors and whether HIV is a recent diagnosis.

Anxiety and alcohol use often co-occur among PHIV (Bing et al., 2001; Chandra, Ravi, Desai, & Subbakrishna, 1998; Lorra Garey et al., 2015) and both are independently associated with decreased medication adherence and viral suppression in PHIV (Chander et al., 2006). While anxiety is prevalent among PLWH, and often co-occurs with alcohol use, most studies examining the relationship between alcohol use and mental health symptoms among PHIV have focused on depression (L. Garey et al., 2015; Havlik, Brennan, & Karpiak, 2011; L'Akoa R, Noubiap, Fang, Ntone, & Kuaban, 2013; Sullivan, Goulet, Justice, & Fiellin, 2011; Sullivan et al., 2008; E. C. Williams et al., 2014). Research examining the relationship between anxiety and alcohol use among PHIV has been very limited (Chander et al., 2006; Lorra Garey et al., 2015). Even scarcer are studies that examine these relationships targeting WHIV. Furthermore, most existing studies in this area are cross-sectional (Bing et al., 2001; Chandra et al., 1998; Lorra Garey et al., 2015). However, because WHIV change their alcohol use patterns over time (Cook et al., 2013), existing studies may not have captured the full picture. Understanding the relationship between change in anxiety and change in alcohol use among WHIV may help promote gender-specific interventions that address both anxiety symptoms and alcohol use, ultimately reducing adverse outcomes associated with the two substances in this population.

Retention in care

Engagement in the medical care system for clinical appointments and treatment, is one step in the HIV Care Continuum (Kay et al., 2016) that is import for people living with human immunodeficiency virus (PHIV) to suppress viral load (Robbins et al., 2007; Sethi, Celentano, Gange, Moore, & Gallant, 2003) and decrease likelihood of death (Giordano et al., 2007; S. H. Lee et al., 2013; Mugavero et al., 2009). The extent of engagement was measured by retention in care (RIC) in three ways including medical visits at defined intervals such as the Institute of Medicine (IoM) index and the Department of Health and Human Services (DHHS) indicator (Rebeiro et al., 2014), missed clinical visits (Mugavero et al., 2014), or both (Horstmann, Brown, Islam, Buck, & Agins, 2010). In the US, unfortunately, a significant proportion of PHIV have poor engagement in HIV care (Mugavero, Amico, Horn, & Thompson, 2013; Robbins et al., 2007), even among those in Veteran Affairs Hospitals or Clinics where few financial barriers exist (Giordano et al., 2007). Rates of non-retention in care (RIC) among PHIV are high among existing studies,

ranging from 11% to 42% depending on socio-demographic, behavioral, and health profiles of the study population and approaches to measuring RIC (Giordano et al., 2007; Monroe et al., 2016b; Robbins et al., 2007; Yang, Yan, Liu, Huang, & Long, 2015). Poor RIC is the aftermath of mixed socio-cultural, economic, and health-system factors (Tiruneh, Galarraga, Genberg, & Wilson, 2016). According to previous studies, predictors of poor engagement in care include initiating ART at a young age (≤ 30 years), absence of non-HIV related comorbidities, high baseline CD4 cell count (>300 cells/μL) (Robbins et al., 2007), and low education level (Tiruneh et al., 2016; Yang et al., 2015). In addition, in the qualitative part of a mixed-method study, researchers identified fear of stigma, care dissatisfaction, use of holy water (symbolizing spiritual blessing), and economic constraints to be factors that hindered RIC among PHIV (Tiruneh et al., 2016).

Alcohol use, mental health symptoms, and retention in care among WHIV

At-risk drinking for general population is defined as drinking >1 drinks (one drink contains 14 grams of pure alcohol) per day for women (National Institute on Alcohol Abuse and Alcoholism, 2016). For persons with comorbid conditions such as HIV, there may be increased risk for adverse outcomes even at lower levels of consumption (Bonacini, 2011). Although alcohol use was found to be associated with medication nonadherence (Beer & Skarbinski, 2014; Braithwaite et al., 2005; Carrico, Woolf-King, Neilands, Dilworth, & Johnson, 2014; Chitsaz et al., 2013; Conen et al., 2009; Herrmann et al., 2012; Holmes, Bilker, Wang, Chapman, & Gross, 2007; King et al., 2012; Lima et al., 2014; Ohl et al., 2013; Parsons, Rosof, & Mustanski, 2008; E. C. Williams et al., 2014; Woolf-King, Neilands, Dilworth, Carrico, & Johnson, 2014) and delayed treatment (Koirala et al., 2017) among PHIV, there have been limited studies examining the effects of alcohol use on the likelihood of attending HIV clinical visits in this population (Koirala et al., 2017; Mugavero et al., 2013). There have been even fewer studies that examine this issue among women living with HIV (WHIV). This problem needs to be further studied because 1) drinking is more prevalent among WHIV than women not living with HIV (Neblett et al., 2011); 2) women are more vulnerable to the effects of alcohol than men due to decreased metabolism and lower proportion of water in their body (Cole-Harding & Wilson, 1987; Frezza et al., 1990); 3) women have an increased likelihood of delaying alcohol overuse treatment (Green et al., 2001).

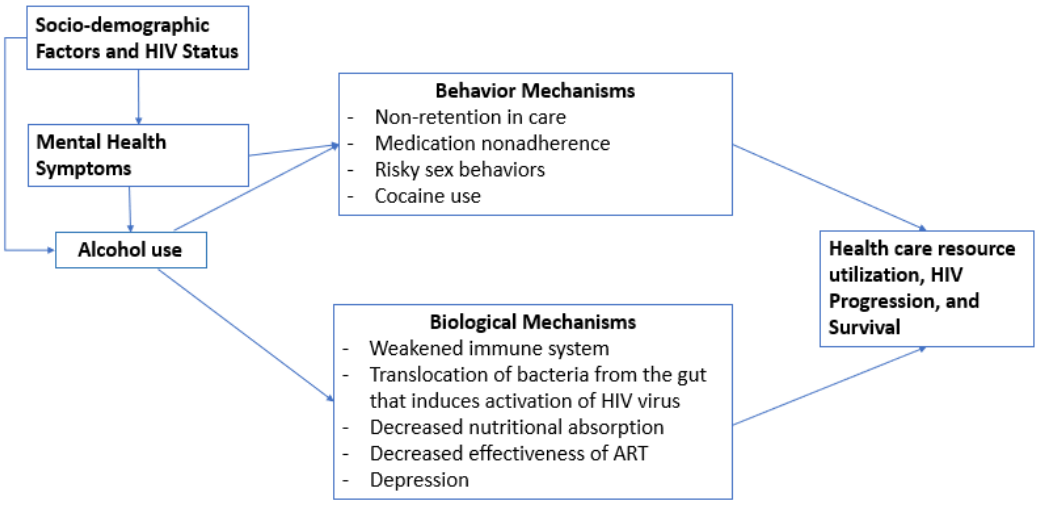
Another issue that needs to be specially attained to about WHIV is that metal health symptoms such as anxiety and depression are more prevalent among women compared with men in the general population and in the HIV-infected population (Chander & McCaul, 2003; McLean et al., 2011; Saadat et al., 2015; van den Heuvel et al., 2013). Those symptoms may negatively affect HIV-related

outcomes in this population (Chander et al., 2006). Although there are extensive literature demonstrating the negative relationship between mental health symptoms and medication adherence, there have not been much studies examining the relationship between mental health symptoms and likelihood of attending HIV clinical visits among PHIV, especially WHIV (Zuniga, Yoo-Jeong, Dai, Guo, & Waldrop-Valverde, 2016).

Understanding the relationship between alcohol use, mental health symptoms such as depression and anxiety, and likelihood of attending HIV clinical visits among WHIV is important to improve retention in care, which is important given the disproportionately high and increasing HIV prevalence among women (Walter, Lundgren, Umez-Eronini, & Ritter, 2016). It may also help promote gender-specific alcohol and mental health symptoms reduction interventions that reduce alcohol use, mental health symptoms, and improve likelihood of attending HIV clinical visits among WHIV.

Conceptual framework

The conceptual framework utilized in my dissertation was the modified Potential Mechanism of HIV Progression framework (Hahn & Samet, 2010). According to this modified framework, living with HIV and socio-demographic factors promote the development of mental health symptoms such as anxiety among PHIV. Anxiety then promotes PHIV to use alcohol. Then, there are two basic mechanisms of how alcohol use contributes to progression of HIV disease- biological mechanisms and behavioral mechanisms (Hahn & Samet, 2010). Biologic effects include weakened immune system (Szabo & Mandrekar, 2009), translocation of bacteria from the gut that induces the activation of HIV virus (Kumar et al., 2005), decreased nutrition absorption (Watzl & Watson, 1992), and decreased effectiveness of ATR (Lieber & DeCarli, 1970). Behavioral effects include decreased ART adherence, increased non-retention in care, and a high correlation between alcohol use and illicit substance use (Braithwaite et al., 2005). The two mechanisms lead to increased HIV progression and decreased survival among PHIV.



Theoretical Framework: Modified Potential Mechanism of HIV Progression Framework (Hahn & Samet, 2010)

Source of data

Data of the dissertation came from two concurrently recruited cohorts of WHIV. One was a randomized controlled trial (RCT) designed to test the effectiveness of a brief alcohol intervention (BI) among WHIV with baseline at-risk drinking (defined as 8 or more drinks/week, 2 or more binge drinking episodes [defined as 4 or more drinks/occasion] in the past six months, or TWEAK score ≥2) (Chander, Hutton, Lau, Xu, & McCaul, 2015). The second cohort was a concurrently recruited sample of WHIV without at-risk drinking at baseline from the same clinic (Barai et al., 2016). The parent studies were registered at clinicaltrials.gov: NCT00127231 and were approved by the Johns Hopkins Medicine Institutional Review Board.

Participants were recruited between March, 2006 and September, 2010 through several methods, including clinic flyers, provider referral, waiting room recruitment, and review of drinking data obtained from an audio-computer-assisted-self-interview (ACASI) routinely administered to patients who have consented to enroll in the HIV Clinical Cohort every six months (Chander et al., 2015). Parent study inclusion criteria included women who 1) had a confirmed HIV infection; 2) received outpatient care at the Johns Hopkins HIV Clinic; 3) were 18 years of age or older; 4) were not receiving treatment for an alcohol use disorder (AUD); 5) not pregnant; and 6) had no history of psychosis at the time of enrollment. Women in the RCT had visits at baseline and three, six, and twelve months post-enrollment; women in the non-at-risk drinking cohort had visits at baseline, and six, and twelve months post-enrollment. For the purpose of this study, we used data at baseline, six months, and twelve months post-enrollment for both cohorts.

Chapter 2: Is Alcohol Use Associated with Increased Risk of Developing Adverse Health Outcomes Among Adults Living with Human Immunodeficiency Virus: A Systematic Review

Abstract

Background: Alcohol use is associated with many HIV-related behaviors that are associated with increased risk of reinfection, transmission, and poorer health outcomes in people living with HIV (PHIV). The population of middle aged and older PHIV is growing due to increased life longevity and aging trend.

Methods: A systematic review across three databases was conducted to evaluate existing studies that examined the association between alcohol use and medication adherence, high-risk sex behaviors, HIV progression, depression, resource utilization, and survival among studies of PHIV with an average age of 40 and above.

Results: Among the included 47 studies, most found a positive association between alcohol use and depression, risky sex behaviors, and resource utilization as well as a negative association between alcohol use and medication adherence among PHIV. The association between alcohol use and response to treatment was variable. The association between alcohol use and survival warrants further study due to lack of existing studies.

Conclusions: The results of this review support that alcohol use negatively impacts middle aged and older PHIV in many aspects; however, there are lack of studies exclusively targeting older PHIV and more relevant studies in the future are needed.

Key words: alcohol use; human immunodeficiency virus; health outcomes; HIV progression; medication adherence; sex behavior; depression; survival; healthcare utilization; elderly

INTRODUCTION

At-risk drinking, defined here as drinking above the recommended limits (no more than 4 drinks in one day for men [3 for women] and no more than 14 drinks in one week for men [7 for women]) is associated with adverse health outcomes in the general population ("Drinking levels defined," 2015). For persons with HIV [PHIV], they may face increased risk even at lower levels of consumption (Bonacini, 2011). For PHIV, alcohol use has been associated with not only increased risk for adverse physical outcomes such as liver damage (Barve et al., 2010) and more rapid virus growth (White & Hingson, 2013), but also with increased risk of depression (Rotheram-Borus, Tomlinson, Le Roux, & Stein, 2015), decreased medication adherence (Braithwaite et al., 2005), and increased engagement in high risk sexual behaviors (Neblett et al., 2011).

In one study with PHIV aged 50 and over, 57% of participants reported drinking alcohol in the past year, and 7% had severe unhealthy drinking (AUDIT-C>7) (Williams et al., 2014). Thus the use of alcohol in PHIV is a concern not only for younger adults but also for those in older cohorts. With the development of antiretroviral therapy (ART), PHIV now have a longer life expectancy if they receive proper treatment. The median survival for PHIV aged 50 years and above receiving treatment increased from 11.8 years during 1996-1999 to 22.8 years during 2006-2014 (Legarth et al., 2016). Almost one in five PHIV are aged 55 or older ("Drinking levels defined," 2015). This increased longevity has resulted in a similar trend that is occurring globally with a growing number of PHIV aged 40 and above ((UNAIDS), 2013).With advancing age, age-related changes occur, such as decreased memory and cognitive abilities that add to the challenges of properly managing HIV. Moreover, older PHIV are medically more complex than younger counterparts (Williams et al., 2014), including being more likely to suffer from severe symptoms, concurrently having other chronic comorbidities, taking multiple medications, and having increased risks of liver toxicity (Centers for Disease Control and Prevention, 2014). The impact of drinking in this population is probably compounded by these existing conditions. Even the general population, as they age, become

more vulnerable to the negative effects of drinking. However, most existing studies targeted mainly the younger population rather than older population with HIV (Williams et al., 2014).

We found no systematic review of the literature examining the association between alcohol use and health outcomes targeting older PHIV. Although primary research on alcohol use and its associated outcomes exclusively targeting this age group are also lacking (Neblett et al., 2011), there is enough published research where the average age of the participants was 40 and above that allowed us to conduct a review on this issue. In an attempt to capture a population with a greater proportion of middle aged and older adults, we conducted a literature review that only included studies where the average age of the participants was 40 and above. The purpose of this systematic review was to evaluate existing studies on the association between alcohol use and medication adherence, engagement in high risk sex behaviors, resource utilization, HIV progression, depression, and survival in studies that included PHIV with an average age of 40 and above. Because alcohol use is a modifiable behavior, understanding the relationship between alcohol use and these variables can lead to the development of interventions tailored to levels of alcohol use to promote better health outcomes among the growing number of middle aged and older PHIV.

REVIEW

Data sources and search strategy

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (Moher, Liberati, Tetzlaff, Altman, & Group, 2010). Three databases (MEDLINE, EMBASE, and CINHAL) were utilized with the help of a master's prepared librarian. Because different databases possessed unique subject headings, each of the three databases was searched independently. The search terms used on MEDLINE were summarized on an online version of Table 1.

Table 1 *Medline Search Terms*

A	(hiv infections[mh] OR hiv[mh] OR hiv[tw] OR hiv-1[tw] OR hiv-2[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immune-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])))
B	(("Alcoholism"[Mesh]) OR "Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR alcohol drink* [tw] OR alcohol* [tw] OR alcohol consumpt* [TW] OR alcohol intake* [tw] OR alcohol abuse [tw]))
C	AND (middle aged [mh] OR aged [mh] OR "middle age" OR "middle aged" OR elderly [tiab] OR senior* [tiab])
Overall	A AND B AND C

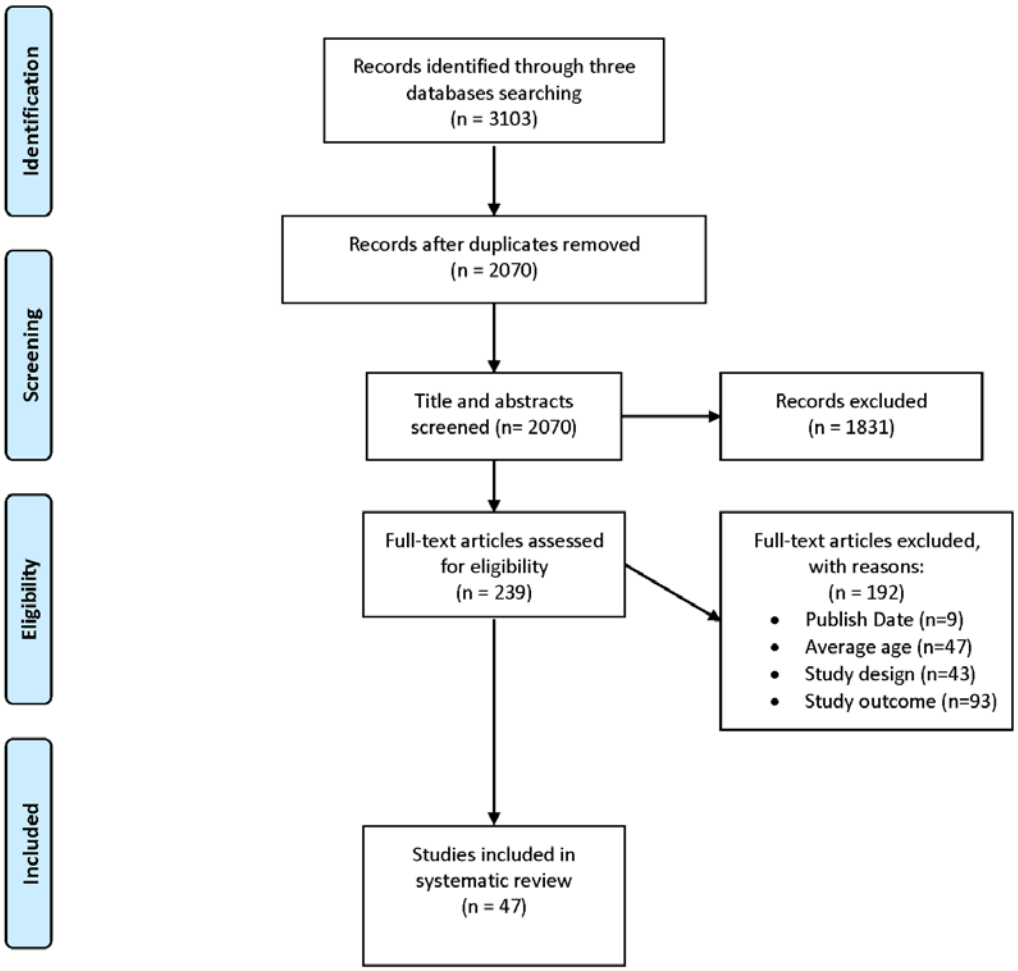
Studies were considered for inclusion if they met the following criteria: (1) descriptive studies containing primary data; (2) average age of the HIV-positive participants in the study was 40 or above; (4) the studies were published in English between 2005 and 2015; (5) examined the impact of alcohol use among PHIV in areas of medication adherence or ART treatment response or depression or/and sex behaviors or survival. Studies that were not published in English or published before 2005 or not primary studies were excluded. The time period between 2005 and 2015 was chosen because literature older than this period would not have reflected more recent advances in ART. Studies in which researchers aimed to assess complications of HIV, such as tuberculosis and pneumonia, were also excluded.

Search results

The process for study selection was conducted in two stages: The first stage included an initial screening of titles and abstracts against the predetermined inclusion and exclusion criteria to identify relevant articles by two researchers. Following this, an evaluation of the full articles of those included studies was conducted. An initial search across the three databases identified 3,103 articles

(1,555 articles on MEDLINE, 1048 on EMBASE, and 500 on CINAHL). After removal of duplicates (n=1033) and review of titles and abstracts, 239 were considered for potential inclusion. After full text reviews, 47 articles were excluded due to unmet criteria about the average age of the participants. Nine studies were excluded due to a publication date prior to 2005. Forty-three studies were excluded due to unmet criteria about study design. Ninety-three studies were excluded due to the fact that those studies did not look at the outcomes identified by the inclusion criteria. Finally, 47 articles were included for this systematic review. Figure 1 presents a flowchart depicting the selection of the studies based on the PRISMA 2009 Guidelines (Figure 1) (Moher et al., 2010).

Figure 1 Flow Chart of article selection based on 2009 Prisma Guideline



Data extraction

Information regarding author, publication date, study location, study design, purpose of the study, inclusion criteria, sample size, average or median age of the participants, outcomes measured, main findings, and limitations were manually extracted for each of the 47 studies (Table 2). To ensure the accuracy of the information, the content was double-checked by a second researcher. Any disagreement was resolved by a third researcher.

Assessment of the methodological quality

The methodological quality of the included studies was assessed based on the modified version of Research Evidence Appraisal Tool developed by Johns Hopkins Nursing Evidence-Based Practice: Model and Guidelines (Table 3) (Sandra Dearholt & Dang, 2012). Rigor of the sampling strategy, time of publication, purpose of the study, validity and reliability of the instrument, rigor of statistical analysis, and discussions of the conclusions and limitations of the study were assessed for each of the included papers and an overall quality rate was generated. High-quality papers were defined as offering consistent and generalizable results, sufficient sample size, adequate control, rigorous statistical analysis, and consistent recommendations based on research findings. Good-quality papers were defined as offering reasonably consistent results, sufficient sample size for the study design, reasonable statistical analysis, and rationally consistent recommendations based on research findings. Low-quality papers were defined as offering little evidence with inconsistent results, insufficient sample size for the study design, and conclusions that cannot be drawn.

Measures of key variables

Alcohol use

Since alcohol use is the main variable in this review and the way to measure alcohol use varied widely in the literature, it is important to understand how alcohol use was measured and defined among the included studies to compare their results. Among included studies, 16 studies used tools or

instruments focusing on screening for an AUD (Altice et al., 2011; Baum et al., 2010; Chitsaz et al., 2013; L'Akoa R, Noubiap, Fang, Ntone, & Kuaban, 2013; Lima et al., 2014) or a diagnosis of AUD (Erickson, Becker, Shaw, Kasper, & Keynan, 2015; Gordon et al., 2006; Heinz, Fogler, Newcomb, Trafton, & Bonn-Miller, 2014; Henrich, Lauder, Desai, & Sofair, 2008; Justice et al., 2006; Kraemer et al., 2006; Obel et al., 2011; Ohl et al., 2013; Palepu et al., 2008; Samet et al., 2007; Sullivan, Goulet, Justice, & Fiellin, 2011). In the rest of the studies, alcohol use was defined related to at-risk use. Fifteen studies used AUDIT or AUDIT-C questionnaire that placed the participants into different categories such as non-hazardous drinking, hazardous drinking, problem drinking or used the score as a continuous variable to indicate the extent of risky drinking (Carrico, Woolf-King, Neilands, Dilworth, & Johnson, 2014; Garey et al., 2015; Gordon et al., 2006; Heinz et al., 2014; Jacob, Blonigen, Upah, & Justice, 2013; Justice et al., 2006; Justice et al., 2016; Kader, Seedat, Govender, Koch, & Parry, 2014; Kalichman et al., 2014; King et al., 2012; Malbergier, Amaral, & Cardoso, 2015; Parsons, Rosof, & Mustanski, 2008; Sullivan et al., 2011; Williams et al., 2014; Woolf-King, Neilands, Dilworth, Carrico, & Johnson, 2014); three studies used a validated calendar or Timeline Follow Back (TLFB) that categorized participants into heavy or non-heavy drinkers (Braithwaite et al., 2005; Samet et al., 2007; Sullivan et al., 2008); twelve studies used self-reported alcohol use (Arasteh & Des Jarlais, 2009; Barta et al., 2008; Barta, Tennen, & Kiene, 2010; Beer & Skarbinski, 2014; Chaudhry et al., 2011; Conen et al., 2009; Cunningham, Sohler, Berg, Shapiro, & Heller, 2006; Hasse et al., 2010; Havlik, Brennan, & Karpiak, 2011; Herrmann et al., 2012; Josephs et al., 2010; Kee et al., 2015; Sullivan et al., 2011); one study examined treatment services review (Stein et al., 2005); two studies used Audio-Computer Assisted Self-interviews (Hutton et al., 2013; Kowalski et al., 2012); one study used an additional severity index (Mugavero et al., 2006); one used a combination of different measures (Miguez-Burbano, Lewis, Fishman, Asthana, & Malow, 2009). Thus, among the included studies, different measures and definitions of alcohol use were adopted with no consistent methods across studies, which hampered our ability to incorporate and compare

study findings. How alcohol use was measured and defined in the included studies were summarized in Table 4.

Medication adherence

Sixteen studies evaluated medication adherence, including self-reported 30 day adherence to ART (Braithwaite et al., 2005; Williams et al., 2014), the number of days of antiretroviral drugs dispensed divided by the number of days on antiretroviral therapy (Lima et al., 2014; Ohl et al., 2013), how often a dose of medication was missed in the previous four weeks (Conen et al., 2009), the adherence measure developed by the AIDS Clinical Trials Group (Beer & Skarbinski, 2014; Carrico et al., 2014; King et al., 2012; Woolf-King et al., 2014), achievement of >95% ART adherence (Chitsaz et al., 2013; Holmes, Bilker, Wang, Chapman, & Gross, 2007), the MED-OUT index (Ohl et al., 2013), cell-phone-based pill counts (Kalichman, Cain, & Simbayi, 2010; Mugavero et al., 2006), modified TLFB (Braithwaite et al., 2005), and at least 95% of all doses taken on a single day based on TLFB (Parsons et al., 2008).

Risky sex behaviors

Seven studies assessed risky sex behaviors, including condom use (Chaudhry et al., 2011; Stein et al., 2005), multiple partners (Stein et al., 2005), vaginal/anal sex, partners' HIV status (Hutton et al., 2013), having sex with stable partners whose HIV status was reported to be negative or unknown or with occasional partners (Barta et al., 2008; Hasse et al., 2010), number of occasions in which they engaged in anal or vaginal sex for the period "last night" and the number of each of these occasions in which participants used a condom "from start to finish" (Barta et al., 2008; Barta et al., 2010), and the proportion of times condoms/female condoms were used during sexual activities (Arasteh & Des Jarlais, 2009).

Healthcare resource utilization

Eight studies assessed resource utilization including outpatient visits, mental health visits, emergency department visits (Cunningham et al., 2006; Josephs et al., 2010), inpatient hospitalizations (Cunningham et al., 2007; Kraemer et al., 2006), whether the participant had a regular doctor (Cunningham et al., 2006), number of healthcare visits in the past six months (Gordon et al., 2006), medical disease profile (Justice et al., 2016), delayed treatment (Conen et al., 2009), and number of missed clinical appointments (Erickson et al., 2015).

HIV progression

Thirteen studies measured changes in viral load or CD4 cell count (Altice et al., 2011; Baum et al., 2010; Carrico et al., 2014; Heinz et al., 2014; Henrich et al., 2008; Kader et al., 2014; King et al., 2012; Kowalski et al., 2012; Lima et al., 2014; Malbergier et al., 2015; Miguez-Burbano et al., 2009; Samet et al., 2007; Woolf-King et al., 2014). One study measured changes of thymus size (Miguez-Burbano et al., 2009). One study measured severity of HIV-related symptoms, such as fatigue, physical symptoms, mood disturbance (Heinz et al., 2014).

Depression

Seven studies measured depression, using measurements of the Patient Health Questionnaire (L'Akoa R et al., 2013; Sullivan et al., 2011; Williams et al., 2014), Center for Epidemiologic Studies Depression Scale (Havlik et al., 2011; Sullivan et al., 2008), Beck Depression Inventory (Kee et al., 2015), and The Inventory of Depression and Anxiety Symptoms (IDAS) (Garey et al., 2015).

Survival

Three studies evaluated survival, including survival from age 25 to 65 years (Obel et al., 2011), hospital mortality (Palepu et al., 2008), and all-cause mortality (Justice et al., 2006).

RESULTS

A total of 135,345 participants were included in the 47 studies. Thirty-eight studies included PHIV only and nine studies included both PHIV and non-infected adults. The sample size of each individual study ranged from 116 to 20,301, with the majority ranging between 400 and 1,000. Three studies were conducted in Canada (Erickson et al., 2015; Lima et al., 2014; Palepu et al., 2008), one in Switzerland (Conen et al., 2009), one in Cameroon (L'Akoa R et al., 2013), one in Korea (Kee et al., 2015), one in Australia (Herrmann et al., 2012), one in South Africa (Kader et al., 2014), and one in Denmark (Obel et al., 2011). The remaining 28 studies were conducted in the U.S. The date of publication ranged from 2005 to 2015. Fifteen studies were longitudinal studies and 32 were cross-sectional. The mean age of participants in the studies ranged from forty (L'Akoa R et al., 2013; Stein et al., 2005) to above fifty (Williams et al., 2014).

Alcohol use and medication adherence

Thirteen studies (Beer & Skarbinski, 2014; Braithwaite et al., 2005; Carrico et al., 2014; Chitsaz et al., 2013; Conen et al., 2009; Herrmann et al., 2012; Holmes et al., 2007; King et al., 2012; Lima et al., 2014; Ohl et al., 2013; Parsons et al., 2008; Williams et al., 2014; Woolf-King et al., 2014) assessed the association between alcohol use and medication adherence. All except two (Kalichman et al., 2014; Williams et al., 2014) found a negative relationship between the two variables. However, the study done by Williams et al. (Williams et al., 2014) yielded opposite findings and indicated that thirty-day ART adherence was not associated with alcohol use or alcohol use severity among 447 PHIV aged 50 and above with suboptimal adherence (non-adherence was defined as missing >1.5 days of medication or taking medications 2 hours early or late on >3 days in the 30 days prior to screening). It might be due to the fact that suboptimal adherence to ART was an inclusion criterion in that study; thus, its findings did not correspond with those in other studies including PHIV with a wide range of level of ART adherence. Another study did not find a

significant overall association between alcohol use and adherence to ART among PHIV; however, alcohol use was found to be significantly associated with nonadherence among participants who did not have sustained viral suppression (Kalichman et al., 2010). In addition, two studies found that even alcohol use of the partners of PHIV had an impact on medical adherence among HIV-infected men who have sex with men (MSM). HIV-infected MSM participants with partner-abstainers versus partner-drinkers had less self-efficacy to persevere in HIV treatment and reported lowered adherence (Carrico et al., 2014; Woolf-King et al., 2014).

Alcohol use and depression

A positive correlation between alcohol use and depression in PHIV with an average age 40 and above was found in seven studies (Garey et al., 2015; Havlik et al., 2011; Kee et al., 2015; L'Akoa R et al., 2013; Sullivan et al., 2011; Sullivan et al., 2008; Williams et al., 2014); however, the associations varied based on participants' drinking profiles. Williams et al. found that the prevalence of positive depression screening was the most common among PHIV aged 50 and above with severe unhealthy drinking (definitions based on AUDIT C score: drinking in past year [0], low-level drinking [1-3], mild-moderate unhealthy drinking [4-6], and severe unhealthy drinking [scores ≥7]) (Williams et al., 2014). However, Sullivan et al. found that after adjusting for other variables, only current alcohol dependence -defined by meeting diagnostic criteria in the past 6 months and assessed using the reference standard Composite International Diagnostic Interview- was independently associated with more depressive symptoms in PHIV with current or past alcohol problems (Sullivan et al., 2008). Sullivan, L et al. in a longitudinal study of U.S. Veterans suggested that depressive symptoms were significantly higher among hazardous and binge drinkers than in past and nonhazardous drinkers LWHIV, (Binge drinkers were defined as consuming 6 or more drinks on one occasion 3 or more times during the past year. Hazardous drinkers were defined by an AUDIT score of 5 (females) or 7 (males) or more (Sullivan et al., 2011). The differences in the results of the three

studies may be attributable to different inclusion criteria and how alcohol use was categorized in those studies. The first study only recruited PHIV aged 50 and above; the second study recruited PHIV with current or past alcohol problems; the third study recruited U.S. Veterans which mostly consisted of men with current or past alcohol problems. Although their results varied, all seven studies agreed that alcohol use and depression were positively correlated in some way.

Alcohol use and risky sex behaviors

Seven studies examined the relationship between alcohol use and risky sex behaviors; all found a positive association between the two variables (Arasteh & Des Jarlais, 2009; Barta et al., 2008; Barta et al., 2010; Chaudhry et al., 2011; Hasse et al., 2010; Hutton et al., 2013; Stein et al., 2005). Besides unprotected sex (Arasteh & Des Jarlais, 2009; Barta et al., 2008; Barta et al., 2010; Chaudhry et al., 2011; Hasse et al., 2010; Hutton et al., 2013; Stein et al., 2005). Risk behaviors found to be positively associated with alcohol use included engaging in anal sex, engaging in insertive anal sex among gay/bisexual men (Hutton et al., 2013), having unprotected sex with a causal partner (Arasteh & Des Jarlais, 2009), and having multiple partners (Hutton et al., 2013; Stein et al., 2005).

Alcohol use and healthcare resource utilization

Seven studies examined the association between alcohol use and healthcare resource utilization among PHIV (Conen et al., 2009; Cunningham et al., 2006; Cunningham et al., 2007; Erickson et al., 2015; Gordon et al., 2006; Josephs et al., 2010; Justice et al., 2016; Kraemer et al., 2006); five found a positive association between the two variables (Cunningham et al., 2006; Cunningham et al., 2007; Josephs et al., 2010; Kraemer et al., 2006). Alcohol use was found to be positively associated with emergency department visits, hospitalizations (Cunningham et al., 2007; Josephs et al., 2010; Kraemer et al., 2006), incidence rates for outpatient and mental health visits

(Kraemer et al., 2006), likelihood of having a regular doctor (Cunningham et al., 2006), and concurrent presence of various medical diseases such as hypertension, diabetes, obstructive pulmonary disease, and bacterial pneumonia (Justice et al., 2016). Two studies found that alcohol use was associated with suboptimal healthcare utilizations including missed appointments (Erickson et al., 2015) and fewer outpatient visits (Gordon et al., 2006). Conen et al. found that alcohol use was not associated with delayed treatment (defined as percent of treatment-naïve individuals with CD4+ T-cell count <200 cells/ul across alcohol consumption categories) (Conen et al., 2009).

Alcohol use and HIV progression

Fourteen studies examined the association between alcohol use and HIV progression. Five studies (Altice et al., 2011; Conen et al., 2009; Kalichman et al., 2014; Kowalski et al., 2012; Samet et al., 2007) found that the association between alcohol use and HIV surrogate markers (CD4 cell or viral load) was not significant. Seven studies (Baum et al., 2010; Heinz et al., 2014; Henrich et al., 2008; Kader et al., 2014; Lima et al., 2014; Malbergier et al., 2015; Woolf-King et al., 2014) found a negative association between alcohol use and response to treatment, including a smaller CD4 cell and viral load change from baseline after starting ART (Henrich et al., 2008; Lima et al., 2014), significant CD4 decline (Baum et al., 2010), lower CD4 count (Kader et al., 2014), greater HIV symptom severity such as fatigue, physical symptoms, and mood disturbance (Heinz et al., 2014), more likely to have CD4 cell count ≤200/mm3 (Malbergier et al., 2015), and higher odd of detectable viral load (Baum et al., 2010; Woolf-King et al., 2014). Moreover, in one study, the types of alcohol had an impact on HIV progression: liquor was associated with thymus deterioration and thus with poorer viro-immune outcomes after HAART than wine and beer. However, it is unclear why liquor is riskier than wine and beer (Miguez-Burbano et al., 2009). In addition, two studies found that even alcohol use of partners of PHIV had an impact on treatment response among men who have sex with

men (MSM) living with HIV. MSM participants with partner-abstainers versus partner-drinkers had a lower adherence and a higher viral load (Carrico et al., 2014; Woolf-King et al., 2014).

Alcohol use and survival

Three longitudinal studies examined the association between alcohol use and survival but yielded conflicting results. One study found that drug and alcohol dependence (diagnosis based on ICNARC code) was not independently associated with hospital mortality in PHIV admitted to the ICU (Palepu et al., 2008); however, the other two studies examining various levels of alcohol use yielded opposite findings. The Danish nationwide-population-based cohort study found that in PHIV with alcohol abuse (diagnosis based on ICD code) had decreased survival from age 25 to 65 years than those without alcohol abuse (Obel et al., 2011). In a Veterans Aging Cohort Study (VACS), risks of mortality and physiologic injury were higher among those with higher AUDIT-C (>3) compared to those with lower AUDIT-C (1-3) (Justice et al., 2016). The inconsistent results may be attributed to different inclusion criteria. The first study ascertained participants from ICU admissions; thus, their HIV symptoms or other comorbidities were probably more severe than participants in the second and third study.

DISCUSSION

Although the number and proportion of PHIV aged ≥40 years old has been increasing rapidly, the characteristics and impact of alcohol use are under-described in this age group (Williams et al., 2014). To our knowledge, this is the first systematic review on this topic. And it is done with rigor and strict adherence to the Prisma protocol. As such, this study makes a unique and meaningful contribution to the field. Many pioneered HIV studies were included including VACS (Braithwaite et al., 2005; Gordon et al., 2006; Jacob et al., 2013; Justice et al., 2006; Justice et al., 2016; Kraemer et al., 2006; Sullivan et al., 2011), Swiss Cohort study (Hasse et al., 2010; King et al., 2012), Western Australia HIV cohort (Herrmann et al., 2012), the Coping with HIV/AIDS in the Southeast (CHASE)

Study (Mugavero et al., 2006), and Korean HIV cohort study (Kee et al., 2015). We choose to conduct a systematic review rather than meta-analysis because measurements of our variables are so different across studies that it is close to impossible to extract a universal item for each outcome to do a meta-analysis. Moreover, the number of articles retrieved for each outcome is small.

Based on the 47 longitudinal and cross-sectional studies, most studies found a positive association between alcohol use and depression, risky sex behaviors, and healthcare resource utilization, as well as a negative association between alcohol use and medication adherence among PHIV aged 40 and above. The association between alcohol use and response to treatment was variable among the included studies. The association between alcohol use and survival warrant further study due to a lack of pertinent studies. These findings are important given the fact that HIV cohort is aging and number of aged PHIV is increasing.

This review gives directions for future studies in a number of ways. First, certain outcomes such as depression and medication adherence were assessed much more frequently than the outcomes of healthcare resource utilization and survival. Thus, some outcomes have not been examined thoroughly with a focus on the multiple co-existing factors. This may be related to the fact that some outcomes are easier and more feasible to be assessed than others. In addition, results regarding the association between alcohol use and response to treatment have been conflicting among the included studies. Thus, more studies are needed to examine this outcome. Moreover, it is important to study the impact of alcohol use on risky sex behaviors of PHIV with a more advanced age because, although the likelihood of having had any sex in the last 6 months decreased significantly as age increased (Stein et al., 2005), PHIV with an advanced age are still at risk for HIV transmission and reinfection via sex. The included studies on this topic were all cross-sectional studies; thus, it remained unknown whether sex activities changed due to changes of HIV status. Moreover, it is unclear whether alcohol use preceded sex activity or the other way around. Thus, more longitudinal studies are needed on this issue. Moreover, there is lack of studies targeting women LHIV aged 40

and above. Prior studies have demonstrated that women are more vulnerable to the toxic effects of alcohol use than men due to slower gastric metabolism of alcohol and less water contained pound for pound in the body (Cole-Harding & Wilson, 1987). However, many of the included studies targeted men (Carrico et al., 2014; Woolf-King et al., 2014) or mostly consist of men such as VACS (Braithwaite et al., 2005; Gordon et al., 2006; Jacob et al., 2013; Justice et al., 2006; Justice et al., 2016; Kraemer et al., 2006; Sullivan et al., 2011). Future studies need to examine the impact of alcohol use targeting women age 40 and above LHIV. In addition, future studies are needed to follow PHIV long-termly and differentiate those with new onset of alcohol use from those with a long history of alcohol use. Studies have shown that people who started alcohol use after age 45 (late onset) differ from those who started drinking before age 25 (early onset) in many ways. The former group reported fewer detoxification episodes, had lower actual alcohol consumption, and had a higher rate of abstinence in the 12-month follow-up than the late onset group (Wetterling, Veltrup, John, & Driessen, 2003). Furthermore, among included studies, only one study (L'Akoa R et al., 2013) identified newly infected PHIV from general PHIV. The rest of the included studies did not differentiate newly infected PHIV from all other PHIV. As people's behaviors could change as a result of a change of their HIV status (Kalichman et al., 2010), future studies that differentiate newly infected PHIV from PHIV with a diagnosis for a long time are warranted.

This review has several limitations. First, most included studies consist of PHIV aged 40 or above as well as those aged below 40 due to lack of studies targeting PHIV aged 40 and above alone. Thus, the results of those studies were results of PHIV with a mixed range of ages. We tried to overcome this limitation by only including studies where the average age of the participants was 40 and above to ensure that at least a substantial proportion of the participants in this review aged 40 and above. Secondly, how alcohol use was defined and measured varied widely among the included studies, which hampered our ability to compare results. To increase comparability, we summarized how alcohol use was defined and measured among included studies with a clear summary and tables.

We believe that this table is very helpful for people to see how alcohol variable was defined and operationalized among studies of this area. Third, the participants are heterogeneous among the included studies, including hard-to-reach marginalized PHIV (Cunningham et al., 2007), imprisoned PHIV (Chitsaz et al., 2013), HIV-infected MSM (Woolf-King et al., 2014), HIV-infected veterans (Kraemer et al., 2006), and PHIV with illicit drug intake (Lima et al., 2014). Thus, the results of those studies may have limited generalizability to other populations and also limited comparability. Moreover, as we did not have the capacity in our author group to review non-English journals, we included only journal articles published in English in this review. Last but not the least, although we adopted very broad inclusion criteria, age is very often not prominently mentioned in the many studies targeting PHIV and thus they could be missed in this review. Despite of the limitations above, we believe that this review is meaningful given the fact that it illustrates how alcohol use was commonly defined and operationalized in literature, identifies a significant gap in research, and gives much direction for future studies.

CONCLUSIONS

Findings are hypotheses-generating regarding the importance of developing alcohol-related educational interventions tailored to middle aged and older PHIV. It is important to take into account the full continuum of at-risk use of alcohol and the association with poorer outcomes in PHIV. Interventions to reduce alcohol use in the population should include individual level as well as modifiable environmental level risk factors that play a key role in determining the extent of alcohol use for the general population as well as PHIV. Given the findings of this review, clinicians should be more aware of the importance of addressing alcohol use across the continuum of use in PHIV aged 40 and above. Clinicians should incorporate alcohol Screening and Brief Intervention (ASBIRT), an evidence-based practice that includes the use of validated alcohol screening tools, the delivery of brief interventions (Chander, Hutton, Lau, Xu, & McCaul, 2015), and when indicated referral to alcohol treatment services. This has the potential to help reduce the potential negative

outcomes (such as risky sex behaviors, poor survival, and poor response to treatment) associated with at-risk alcohol use in PHIV aged 40 and above. The ultimate goal is to improve quality of life as well as survival in this growing population.

Table 2

Data Extraction of Included Articles

First author, year of publication, country	Study design; sample size	Mean age; age range	Outcomes	Measurement of alcohol use	Purpose	Main Findings	Limitations
Palepu et al., (2008), Canada	longitudinal; 7015	above 41	hospital mortality	ICU admitting diagnosis based on ICNARC codes	To explore if the diagnoses of drug or alcohol dependence and HIV infections, as well as the 2 concurrent diagnoses were independently associated with hospital mortality	Drug and alcohol dependence were not independently associated with hospital mortality.	single geographic area; no HIV confirmation test; patient's disease stage was not characterized by CD4 or HAART exposure. Not all types of substances used were known.
Kraemer et al., (2006), US	longitudinal; 48144	above 47	outpatient visits, emergency department visits, and inpatient hospitalizations	alcohol-related ICD-9-CM codes	To examine the association between alcohol problems and health care services use in HIV infected and HIV uninfected patients	Alcohol problems are associated with greater outpatient, emergency department, and inpatient health care utilization in HIV-infected veterans.	Unable to determine whether the participants were drinkers at time of study
Williams et al., (2014), US	cross-sectional; 447	>50 years old;	drinking status, past-year alcohol treatment, and depression screening	AUDIT-C	To assess alcohol use among older PLWH	Alcohol use was associated with demographics, depression, and substance use history.	Did not assess alcohol use over time. Sample size was relatively small.

Lima et al., (2014), Canada	longitudinal; 537	above 40	virologic response, immunologic response, medication adherence	CAGE questionnaire	To assess the relationship between alcohol and illicit substance use on HAART outcomes	Individuals with a history of both alcohol and injection drug use had a higher likelihood of experiencing the worst immunologic and virologic responses, mostly due to poor adherence.	Certain marginalized populations were over sampled. Alcohol consumption was not measured directly.
Stein et al., (2005), US	cross-sectional; 262	40.7	factors associated with any sexual activity, unsafe sexual activity, and sexual risk	self-reported alcohol consumption	To examine if alcohol was associated with risk taking behavior in HIV infected persons	All measures of alcohol use were significantly associated with any sexual activity and with unsafe sexual behavior.	Nonrandomized sample may limit generalizability. Self-report of results can lead to bias.
Sullivan et al., (2011), US	longitudinal; 2446	50.2; 22-87	depressive symptoms	AUDIT and ICD-9	To evaluate the impact of varying levels of alcohol consumption on depressive symptoms over time in patients with and without HIV infection	HIV-infected and HIV-uninfected hazardous and binge drinkers have depressive symptoms that are more severe than non-hazardous and non-drinkers and similar to those with alcohol abuse or dependence.	The cohort consist of U.S. Veterans who were mostly men. self-report drinking can lead to bias.

Sullivan et al., (2008), US	longitudinal; 400	43; 21-71	depressive symptoms	Composite International Diagnostic Interview (CIDI) and a validated calendar-based method	To examine the impact of alcohol use on depressive symptoms in human immunodeficiency virus infected patients.	Alcohol use was associated with more depressive symptoms in HIV-infected patients with alcohol problems.	Heavy depressive symptoms at baseline may have masked some of the impact of alcohol had on these symptoms.
Burbano et al., (2009), US	longitudinal; 400	between 38.5 and 41.5	viral load and CD4 count	the Physician's guide of the National Institute on Alcohol Abuse and Alcoholism, American Association, CAGE, AUDIT and ADS	To evaluate the impact of hazardous versus non-hazardous alcohol use on the health status of HIV-infected individuals receiving HAART.	Liquor was associated with thymus deterioration and thus with poorer viro-immune outcomes after HAART	The observed significant effects seemed to be small.
Conen et al., (2009), Switzerland	cross-sectional; 6323	42	adherence and HIV surrogate markers	self-reported alcohol consumption	To study self-report alcohol consumption and its association with ART adherence	Higher alcohol consumption in HIV-infected individuals was associated with non-adherence to ART	Could not infer causal relationships. Self-reported information can be biased.
Heinz et al., (2014), US	cross-sectional; 172	48.37	memory functioning and HIV symptom severity	AUDIT test	To examine the impact of problematic alcohol use on cognitive functions among PHIV	Problematic alcohol use was associated with lower total memory functioning	Self-report measurement of HIV symptoms severity can be biased.

King et al., (2014), US	cross-sectional; 356	45.5	self-reported ART adherence, ART adherence self-efficacy, and HIV viral load	AUDIT test	To examine the independent association of individual- and partner-level alcohol use with HIV disease management among men who have sex with men	Abstainers compared to hazardous drinkers, had higher self-efficacy to follow HIV treatment	Cross-sectional studies cannot generate causal relationships. Age, race, and relationship length limit generalizability of the study.
Samet et al., (2007), US	longitudinal; 595	41	CD4 cell count and HIV RNA	validated calendar method	To assess the relation between alcohol consumption and laboratory markers of HIV disease progression	Heavy alcohol consumption negatively impacted the CD4 cell count of HIV infected persons not receiving ART.	Participants were not recruited at the time of seroconversion and followed for their alcohol use, CD4 cell counts, and viral loads over time.
Chitsaz et al., (2013), US	cross-sectional; 1164	42.8	substance use, ART adherence, and HIV treatment outcome	Addiction Severity Index (ASI)	To examine contribution of Substance Use on HIV treatment outcomes and antiretroviral medication adherence among HIV infected population in jail	Alcohol use severity was negatively and independently correlated with medication nonadherence.	Self-report data could be biased. The 30-day pre-incarceration period may introduce bias.
L'akoa et al., (2013), Cameroon	cross-sectional; 100	40.4; 18-62	depression	CAGE questionnaire	To examine the prevalence and correlates of depressive symptoms in PHIV	Probable depressed patients were more likely than those who were not depressed to have experienced alcohol abuse.	Patients from isolated rural areas were not included. The convenience sample of 100 suggested imprecision.

Obel et al., (2011), Denmark	longitudinal; 11333	above 40; 34-53	mortality, viral load, and CD4 count	discharge and diagnoses according to the International Classification of Diseases.	To examine the impact of non-HIV and HIV Risk Factors on Survival in PHIV on HAART	Survival was lower in PHIV with alcohol abuse.	Only PWHIV aged 25–64 were included. Smoking status was not taken into account.
Cunninghan et al., (2006), US	longitudinal; 610	above 40;	ambulatory, emergency department, and inpatient visits	self-reported alcohol use	To examine factors associated with health care utilization in hard-to-reach marginalized PHIV	Emergency department visits were associated with heavy alcohol use.	There are no clear means to identify and recruit hard-to-reach populations who were not in care, or were intermittently in care.
Garey et al., (2014), US	cross-sectional; 94	48.55	depression and anxiety	AUDIT Score	To evaluate hazardous drinking in relation to anxiety and depressive symptoms in PHIV	Hazardous drinking was associated with depressive and anxiety symptoms, and HIV symptoms distress.	Cross-sectional study did not identify mediating factors. Self-report measures were subjective.
Havlik et al., (2011), US	cross-sectional; 1000	55.5;	morbidity and depression	self-report questionnaire	To investigate whether depression in elders LHIV are associated with number and types of comorbidities	Depression was significantly associated with increased alcohol use.	Modest correlations could not infer causality or direction of associations.
Kee et al., (2015), Korea	longitudinal; 840	41.9	depression and anxiety	self-report questionnaire	To determine the level of and factors associated with anxiety and depression among PHIV	Current drinking was associated with increased anxiety and depressive symptoms.	Some factors relevant to outcomes were not considered.

Arastah et al., (2009), US	cross-sectional; 1253	40	sexual risk behaviors	self-report questionnaire	To assess at-risk drinking and injection and sexual risk behaviors of HIV-positive injection drug users entering drug treatment in New York City	At-risk drinkers were more likely to engage in unprotected sex with a casual partner.	No measure of frequency of binge drinking; dichotomous measure of alcohol use was rough.
Barta et al., (2008), US	cross-sectional; 116	45	sexual risk behaviors	self-report alcohol use, Alcohol Dependence Scale (ADS)	To investigate alcohol-involved sexual risk behavior among economically disadvantaged problem drinkers LHIV	Alcohol consumed prior to sex significantly affected rate of unprotected sex.	Cross-sectional design could not infer causality.
Barta et al., (2010), US	cross-sectional; 125	46; 25-65	unprotected sex and sex craving	self-report alcohol use using daily diary	To examine alcohol-involved sexual risk behaviors among economically disadvantaged problem drinkers living with HIV/AIDS	Findings support the moderating effects of high negative affect and sexual craving on the association between alcohol use and unprotected sex	Diary adherence was low. Self-report data might not be accurate.
Chaudhry et al., (2011), US	cross-sectional; 386	45.6	HIV risk behaviors	self-report alcohol use using survey	To explore HIV transmission risk behaviors in PHIV	Alcohol use in previous 30 days was significantly associated with risky sex.	no uniform system of treatment assignment across sites; no randomization of participants
Hasse et al., (2010), US	longitudinal; 7309	median age between 39-43	HIV risk behaviors	Interviewer administered questionnaire	To study the frequency, changes over time, and determinants of unprotected sex among PHIV	Moderate or severe alcohol use was associated with unprotected sex.	uncertainty on accuracy of self-reported information about sexual behavior, illicit drug use, and alcohol consumption

Hutton et al., (2013), US	cross-sectional; 910	between 39-42	risk sex behaviors	audio-computer-assisted-self-interviews	To examine the association between alcohol use and risky sexual behaviors in PHIV	Infrequent drinkers did not differ in sexual risk behaviors from abstainers among PHIV.	Heavy drinking was defined conservatively.
Cunningham et al., (2006), US	cross-sectional; 238	41	access to healthcare	face to face interview	To investigate the associations between specific types of substances of abuse and access to HIV health care	PHIV with binge alcohol use were more likely to have a regular doctor than those without binge alcohol use.	modest sample size; health care access data were from self-report.
Erickson et al., (2015), Canada	cross-sectional; 564	above 40	care outcomes	chart review	To understand the impact of substance use on care outcomes for PHIV in Manitoba	Abused alcohol was associated with missed appointments.	Retrospective study led to potential underreporting of substance use and difficulty in ascertaining multi-substance use.
Gordon et al., (2006), US	cross-sectional; 881	48.7	healthcare utilization	AUDIT	To evaluate the impact of homelessness and alcohol use on utilization of health services among PHIV	Hazardous drinking and current homelessness were associated with <2 outpatient clinic visits.	Multivariable analyses on health care utilization were related to hazardous alcohol consumption but not for more severe forms of drinking.
Josephs et al., (2010), US	cross-sectional; 951	median age 45; 20-85;	emergency department visit	person to person interview	To examine Emergency Department (ED) utilization and clinical and sociodemographic correlates of ED use among PHIV	Social alcohol use was associated with emergency department visit.	self-reported measures of ED utilization; a large proportion of patients had missing CD4 count and HIV-1 RNA data.

Justice et al., (2006), US	cross-sectional; 886	median age 50	medical diseases	AUDIT and ICD-9	To explore whether level of exposure to alcohol is associated with medical disease and whether the association depends upon the proximity of alcohol use	Alcohol use was significantly associated with various medical diseases.	Few women were included. less complete data on drug and cigarette use
Justice et al., (2016), US	longitudinal; 18145	52.5	all-cause mortality and physiologic injury	AUDIT-C	To examine the association between alcohol exposure and mortality in PHIV through July, 2014	PHIV experienced increased mortality and physiologic injury at higher levels of alcohol use compared with lower use.	Accurate measurement of exposure to alcohol was challenging. Non-drinkers were excluded.
Herrmann et al., (2012), Australia	cross-sectional; 152	above 44	alcohol and drug use	Self-reported questionnaire	To ascertain the prevalence of substance use among PHIV in Western Australia	Sessional alcohol consumption was prevalent among drinkers and correlated with both early treatment phase and non-adherence.	not mentioned
Parsons et al., (2008), US	cross-sectional; 272	43.7; 26-66	viral load and CD4 count	AUDIT Score	To investigate temporal and dose response relationships between alcohol use and medication adherence in PHIV with alcohol problems.	Consumption of alcohol significantly and substantially increased the odds of medication nonadherence.	Self-reported alcohol use may underestimate the actual use.

Carrico et al., (2014) US,	cross-sectional; 532	45.8	stimulant use, ART adherence, and HIV viral load	AUDIT	To examine relationship factor as correlates of stimulant use and HIV disease management among men who have sex with men	Partner-level alcohol use was independently associated with greater odd of reporting perfect 3-day ART adherence.	Stimulant use was assessed using self-report measures that did not adequately characterize patterns of use, route of administration, or screening for the presence of stimulant use disorder.
Ohl et al., (2013), US	longitudinal; 20301	45; 39-52	ART adherence	ICD-9	To examine antiretroviral adherence among rural and urban-dwelling veterans LHIV in the US.	Rural veterans were less likely to have an alcohol use disorder; rural veterans had more advanced immune compromise at care entry as evidenced by lower CD4 counts (median CD4 ranging from 300 among urban veterans to 247 among rural-small town/remote veterans	VA healthcare differs from non-VA care, which may limit generalizability of study findings. Veterans with HIV are almost all male.
King et al., (2012), US	cross-sectional; 326	45.9	ART adherence	AUDIT	To investigate the association of nonadherence to ART with potential demographic, psychosocial and substance use variables among PHIV who smoke	Nicotine dependence, illicit drug use, and alcohol use are potentially formidable barriers to ART adherence among PLWHA who smoke.	analysis of cross-sectional data and reliance on self-report data; the ART adherence measure lacks specificity.

Kalichman et al., (2014), US	Cross-sectional; 183	above 45	HIV Viral Load and CD4 Count	AUDIT	To examine alcohol use associated with sustained viral suppression as well as medication adherence among PHIV who drink alcohol and take ART.	Alcohol use was associated with nonadherence among participants who did not have sustained viral suppression	A convenience sample cannot be considered representative of PHIV. Sample came from clinical services that varied in adherence assistance and substance use treatment. Study relied on self-report instruments.
Beer et al., (2014), US	cross sectional; 4217	above 40	HIV Viral Load and ART adherence	Self-report	To assess if self-reported adherence is associated with viral suppression; what factors are independently associated with adherence in PHIV	Factors associated with lower adherence included younger age, female gender, depression, stimulant use, binge alcohol use, greater than once-daily dosing, longer time since HIV diagnosis, and patient beliefs.	Self-reported adherence measure. Residual bias may exist
Braithwaite, R.S., (2005), US	Cross-sectional; 2352	50.1	ART adherence	Timeline Follow Back Modified for Adherence	To determine whether there are temporal and dose-response relationships between alcohol consumption and poor adherence among PHIV	Among veterans in care, self-reported alcohol consumption demonstrates a temporal and dose response relationship to poor adherence.	Adherence was measured with an adapted instrument that did not distinguish antiretroviral from non-antiretroviral drugs. Participants were primarily male and urban population of veterans.

Kowalski, S., (2014), US	Longitudinal; 1107	42; 678-429	CD4 and alcohol use	alcohol use was measured by self-report	To evaluate the longitudinal association of alcohol use with immunologic response to combination antiretroviral therapy (ART) among PHIV	There was no statistically significant difference in CD4 T-cell count by average drinks per drinking day at any frequency of alcohol use irrespective of sex or viral suppression	Sample may not have included the heaviest drinkers. Limited to populations similar to our study sample, which included largely urban, African American, HIV-infected individuals. Alcohol use was measured by self-report
.Jacob et al., (2012), US	cross sectional; 7422	49.4	Depression and drug use	AUDIT, Self-report	To determine the generalizability of these findings to a sample of midlife veterans with quite different characteristics from those previously assessed; specifically, veterans in treatment for HIV and veterans in treatment for non-HIV medical issues.	Both the HIV+ and non-HIV groups exhibited 4 patterns of drinking. SC drinkers had younger ages of onset for drinking and longer duration of smoking. SC drinkers also had the highest rates of cocaine use. Within the HIV+ subsample, SC and LO drinkers increased their drinking after their HIV diagnosis.	Analyses did not contain precise information regarding date of HIV diagnosis. The investigator did not know at what time this occurred.
Malbergier et al., (2014), US	cross-sectional; 438	41.38	Depression and drug use	AUDIT	To assess the association between alcohol and drug use and CD4 cell count among PHIV on ART in an urban HIV reference center.	Alcohol dependence seems to be associated with low CD4 cell count in HIV-positive patients	self-report questionnaire to assess adherence to ART in the past week; the cross-sectional design of this study may impair our capacity to provide definite information

							about cause-and-effect relationships.
Kader et al., (2013), South Africa	cross-Sectional; 1503	35.83	drug use	AUDIT; self-report	To establish the prevalence of hazardous use of alcohol and drug problems among patients attending a representative sample of HIV clinics in Cape Town and to investigate the role of such substance use in health status and disease progression	Hazardous and harmful use of alcohol was a statistically significant and important determinants of lower CD4 counts, TB positive status and the likelihood of patients being on ARVs.	Sample may not be representative of the HIV treatment seeking population across South Africa. Alcohol and drug use was measured by self-reports and were not confirmed by laboratory testing.
Altice et al., (2011), US	cross-sectional; 295	above 43	receiving antiretroviral therapy (ART) and HIV-1 RNA suppression and mean changes in CD4 lymphocyte count	alcohol addiction severity	To determine factors that may contribute to HIV progression	Being on ART was negatively associated with alcohol addiction severity	cross-sectional study design; considerable missing data

Henrich et al., (2007), US	cross sectional; 293	43.2	CD 4 count	charted history of alcohol abuse	To examine the association of alcohol abuse and injection drug use (IDU) with the immunologic and virologic responses to highly active antiretroviral treatment (HAART) in urban community health clinics	many patients at urban health clinics have a history of either injection drug use or alcohol abuse, and that injection drug use is negatively associated with the immunologic response to HAART in urban HIV-infected individuals	It was not possible to differentiate between active and past alcohol abuse or IDU in our study; patients were on different combination antiretroviral therapies, some with protease inhibitors and some without.
Baum et al., (2011), US	longitudinal; 231	42.72	CD4 count, HIV Viral load	alcohol and drug abuse questionnaire	To examine the associations of alcohol use with HIV disease progression, measured by CD4 cell count decline and HIV viral load, in a cohort of PHIV with drug use	Frequent alcohol intake, as well as the combination of frequent alcohol and crack-cocaine, accelerated HIV disease progression	This study was a secondary subset analysis of a longitudinal nutrition study of a cohort of HIV-seropositive alcohol and drug users.
Mugavero et al., (2006), US	cross-sectional; 474	40.6; 20-71	ART adherence	Addiction Severity Index (ASI)	To examine whether lifetime traumatic events including physical and sexual abuse, are associated with antiretroviral nonadherence	Increased severity was not associated with medication adherence	cross-sectional design and self-report adherence to ART

Table 3

Quality Appraisal of Research Studies

1. Did the researcher identify what is known and not known about the problem and how the study will address any gaps in knowledge?	Yes	No	
2. Was the purpose of the study clearly presented?	Yes	No	
3. Was the study conducted within 10 years	Yes	No	
4. Were data collection methods described clearly?	Yes	No	
5. Were the instruments reliable (Cronbach's alpha >=0.7)?	Yes	No	NA
6. Was the validity of the instrument discussed?	Yes	No	NA
7. If tables were presented, was the narrative consistent with the content?	Yes	No	NA
8. Were study limitations identified and addressed?	Yes	No	
9. Were conclusions based on results?	Yes	No	
Quality Rating based on Quality Appraisal			
A High quality: consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on research findings			
B Good quality: reasonably consistent results; sufficient sample size for the study design; some control, and fairly definitive conclusions; reasonably consistent recommendations based on research findings			
C Low quality or major flaws: little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn			

Table 4

Definitions and Measurements of Alcohol Use

Type of Measurement	Instrument	Categories	Study
Alcohol use Disorders (AUD)	ASI	score of addiction severity alcohol	Altice et al., (2011)
	Alcohol and drug abuse questionnaire and medical record	patterns, changes and frequency of use and confirmation by medical record	Baum et al., (2011)
	Alcohol Severity Index (ASI)	alcohol related DSM-IV	Chitsaz et al., (2013)

	Patient chart review	alcohol abuse	Erickson et al. (2015)
	VA administrative diagnosis	alcohol abuse or dependence	Gordon, A et al. (2006)
	Medical record	diagnosis of alcohol abuse	Henrich et al., (2007)
	The Structured Clinical Interview-Non-Patient Version for DSM-IV	alcohol abuse or dependence	Heinz et al., (2014)
	ICD-9 codes	abuse or dependence	Justice et al., (2006)
	Alcohol-related ICD-9-CM codes	alcohol-related diagnoses or complications between October 1, 1998, and September 30, 2003	Kraemer et al., (2006)
	CAGE	no indication of a history of alcoholism(0-1), having an indication of a history of alcoholism (2-3), or having a confirmed history of alcoholism (4)	Lima et al., (2014)
	CAGE	alcohol abuse (≥2)	L'akoa et al., (2013)
	ICD codes	alcohol/drug abuse reported as the route of HIV transmission or hospital contacts before the index date	Obel et al., (2011)
	ICD-9 codes	diagnosis of alcohol use disorder	Ohl et al., (2013)
	The Intensive Care National Audit and Research Council (ICNARC) codes	alcohol or drug dependence at 2 hospitals between January 1999 and January 200?	Palepu et al., (2008)
	Composite International Diagnostic Interview (CIDI)	meeting diagnostic criteria of alcohol dependence in the past 6 months	Samet et al., (2007)
	ICD-9 codes	alcohol abuse or dependence diagnosed in the year prior to or up to six months after the survey date	Sullivan et al., (2011)
	AUDIT	problematic alcohol use (continuous variable)	Heinz et al., (2014)
At-risk alcohol use	AUDIT	alcohol related problems (≥8)	Jacob et al., (2012)
	AUDIT	harmful alcohol use (≥8)	Malbergier et al., (2014)

AUDIT	abstainers (0), nonhazardous (1-7) or hazardous (≥ 8)	King et al., (2014)
AUDIT	hazardous drinkers (≥ 5 for females or ≥ 7 for males)	Sullivan et al., (2011)
AUDIT	abstainers (0), nonhazardous drinkers (1-7), hazardous drinkers (≥ 8)	King et al., (2014)
AUDIT	abstinence or low-risk drinking (0-7), hazardous drinking (8-15), harmful drinking (16-19), and dependence (20-40)	Kader et al., (2013)
AUDIT-C	non-drinking (0), low-level drinking (1-3), mild-moderate Unhealthy drinking (4-6), or severe unhealthy drinking (7-12)	Williams et al., (2014)
AUDIT	hazardous drinking (>8) and non-hazardous drinking (0-8)	Garey et al., (2014)
AUDIT	hazardous drinking (AUDIT score ≥ 8 or reporting binge-drinking)	Gordon et al., (2006)
AUDIT	"hazardous" drinker (≥6 drinks at a time; >14 drinks/week for men or >7 drinks/week for women or an overall AUDIT score > 8) moderate drinker (alcohol use at any time), lifetime abstainer (no record of any alcohol consumption)	Justice et al., (2006)
AUDIT-C	integers of AUDIT-C scores	Justice et al., (2015)
AUDIT	problem level drinking (>8)	Kalichman et al., (2014)
AUDIT	problem level drinking (>8)	Parsons et al., (2008)
AUDIT	cumulative AUDIT score	King et al., (2012)
AUDIT	cumulative AUDIT score	Carrico et al., (2014)
Calendar method	heavy drinking (> 14 drinks per week or ≥5 drinks on a single occasion for men <66 years old; >7 drinks per week or ≥4 drinks on a single occasion for men ≥66 years old and all	Samet et al., (2007)

	women), moderate alcohol use (any drinking less than heavy)	
Calendar method	heavy drinking (> 4 drinks on 1 day or > 14 drinks per week on average for men; > three or > seven drinks for women in the past month)	Sullivan et al., (2008)
Calendar method	abstainers (no alcohol consumption in the previous 30 days); non-binge drinkers (no day on which ≥5 drinks were consumed); binge drinkers (≥5 drinks within a calendar day at least once during the previous 30 days)	Braithwaite, R.S., (2005)
Combination of the Physician's guide of the National Institute on Alcohol Abuse and Alcoholism, American Association, CAGE, AUDIT and ADS	preferring to drink only liquor group, and preferring to drink only beer or wine group	Burbano et al., (2009)
Self-reported alcohol use	light (<20g for women and <40g for men), moderate (20-40g for women and 40-60g for men), or severe health risk (>40g for women and >60g for men)	Conen et al., (2009)
Self-reported alcohol use	binge drinking (5≥drinks in one sitting for men and 4≥drinks in one sitting for women)	Beer et al., (2014)
Self-reported alcohol use	binge drinkers (6 or more drinks on one occasion 3 or more times during the past year)	Sullivan et al., (2011)
Audio-Computer-Assisted-Self-Interviews (ACAIS)	no alcohol use group (no alcohol intake), low use group (alcohol intake < once a month or 1–3 times a month, and never consumed > 5 drinks in a single day), the frequent/binge group (> 5 drinks on any occasion in the last 3 and/or alcohol at least once a week)	Hutton et al., (2013)
ACAIS	average number of alcoholic drinks consumed per drinking	Kowalski, S. (2014)

	day and number of days of alcohol consumption in a week	
Addition Severity Index (ASI)	ASI scores measuring alcohol use in the past 30 days	Mugavero et al., (2006)
Interviewer administered questionnaire	severe (female, 140 g/day; male, 160 g/day), moderate (female, 20–40 g/day; male, 40–60 g/day), and light use (female, 20 g/day; male, 40 g/day)	Hasse et al., (2010)
Person to person interview	hazardous (>14 drinks per week for men and >7 drinks per week for women)	Josephs et al., (2010)
Self-reported alcohol use	alcohol lifetime (yes or no) alcohol in last 3 months (yes or no)	Havlik et al., (2011)
Self-report alcohol use	current drinker (yes or no), ex-drinker (yes or no), non-drinker (yes or no)	Kee et al., (2015)
Self-report alcohol use	at risk drinkers (men > 14 drinks and women > 7 drinks in a week during the prior 6 months)	Arastah et al., (2009)
Self-report alcohol use	number of standard drinks	Barta et al., (2008)
Self-report alcohol use	number of standard drinks using daily diary	Barta et al., (2010)
Self-report alcohol use	lifetime history of alcohol use	Chaudhry et al., (2011)
Self-report alcohol use	alcohol use over a 30-day period (drinks/per week)	Herrmann et al., (2012)
Face-to-face interview	“binge alcohol users” (≥5 drinks on a typical day at least two times per month when they drank alcohol during the past year)	Cunningham et al., (2006)
Treatment Services Review	hazardous drinking (≥1 binge drinking episodes or if the participant exceeded an average of 14 drinks [7 drinks for women] per week)	Stein et al., (2005)

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Chapter 3: Associations between Change in Anxiety and Changes in Alcohol Use among Women with Human Immunodeficiency Virus

Abstract

Background: Anxiety and alcohol use are prevalent among women with HIV (WHIV); however, their relationship has not been well studied.

Methods: In a sample of WHIV, we examined the relationship between change in generalized anxiety (measured with Hospital Anxiety and Depression, Anxiety Subscale [HADS-A]) and changes in alcohol use (measured with Timeline Follow-back) over 12 months using mixed models controlling for age, education, race/ethnicity, partner status, viral load, ART, employment status, depression, and cocaine use.

Results: Among 224 WHIV, the prevalence of GAD differed between women with at-risk drinking (>7 drinks per week) (28.9%) and those without at-risk drinking (20.2%). The former had higher mean depressive symptoms (p=0.047) and anxiety scores (p=0.045) and were more likely to use cocaine (p=0.006). There was no significant correlation between change in anxiety and changes in alcohol use including binge days, drinking days, and number of drinks per drinking day. However, increased cocaine use was associated with increased binge days, drinking days, and number of drinks per drinking day (all $p \leq 0.01$). Decreased cocaine use was associated with decreased number of drinks per drinking day ($P<0.01$). Decreased depression symptoms were associated with decreased binge drinking days (P=0.02) and drinking days (P=0.04).

Conclusions: Prevalence of GAD is high among WHIV, particularly those with at-risk drinking. For these WHIV, changes in cocaine use and depression affect their drinking more than changes in anxiety. Clinicians should incorporate assessment of alcohol use, depression, and cocaine status into routine HIV care for WHIV and provide them with resources and strategies to effectively manage these co-occurring conditions.

Key words: HIV, women, cocaine, depression, alcohol

INTRODUCTION

Alcohol use is prevalent among women with human immunodeficiency virus (WHIV). Among 1123 WHIV in the Women's Interagency HIV Study, 62% reported current alcohol use and 7% reported heavy use (Kelso-Chichetto et al., 2017). At-risk alcohol use among women, defined as ≥4 standard drinks per occasion (one standard drink contains 14 grams of pure alcohol (National Institute on Alcohol Abuse and Alcoholism, 2016)) , or average daily drinking of >1 standard drink, interferes with entry and retention in the HIV care continuum (Kay et al., 2016)-the steps that persons with HIV (PHIV) progress through in order to achieve and maintain viral suppression (Braithwaite & Bryant, 2010; Braithwaite et al., 2005; Erickson et al., 2015; Etienne et al., 2010; Fatch et al., 2013; Gordon et al., 2006; Kelso-Chichetto et al., 2017; S. Lee et al., 2016; Monroe et al., 2016a). These steps include linkage and retention in care, antiretroviral receipt and adherence, and viral suppression. Thus, at-risk drinking may increase the risk of developing adverse health outcomes among PHIV. This problem may be further compounded among WHIV since women are biologically more vulnerable to the effects of alcohol (Cole-Harding & Wilson, 1987; Frezza et al., 1990) and are more likely to delay alcohol treatment compared with men (Green et al., 2001).

Anxiety is more prevalent among women compared with men in the general population and among WHIV compared with un-infected women (Chander & McCaul, 2003; McLean et al., 2011; Saadat et al., 2015; van den Heuvel et al., 2013). HIV-related experiences such as a recent diagnosis of HIV (M.-K. Kee et al., 2015) and greater HIV-related stigma (Kamen et al., 2015) have been associated with increased anxiety symptoms and emotional distress among PHIV. Demographic factors, drug use, and social support are also important predictors of anxiety among PHIV (Catz et al., 2002; M. K. Kee et al., 2015). Anxiety may also have both direct and indirect negative effects on HIV/AIDS progression (Chander et al., 2006). The reported prevalence of anxiety among WHIV

varies widely in the literature (from 1.91% to over 40%) (Goggin et al., 1998; Morrison et al., 2002; Niu et al., 2016) depending on methods of assessment of anxiety (Chander et al., 2006), types of anxiety assessed, and differences in participants' characteristics such as social-demographic factors and whether HIV is a recent diagnosis.

Anxiety and alcohol use often co-occur among PHIV (Bing et al., 2001; Chandra et al., 1998; Lorra Garey et al., 2015) and both are independently associated with decreased medication adherence and viral suppression (Chander et al., 2006). Despite the elevated prevalence of anxiety among PLWH, most studies examining the relationship between alcohol use and mental health symptoms among PHIV have focused on depression (L. Garey et al., 2015; Havlik et al., 2011; L'Akoa R et al., 2013; Sullivan et al., 2011; Sullivan et al., 2008; E. C. Williams et al., 2014). Research examining the relationship between anxiety and alcohol use among PHIV has been very limited (Chander et al., 2006; Lorra Garey et al., 2015). Even scarcer are studies that examine this issue targeting WHIV. Most existing studies in this area are cross-sectional (Bing et al., 2001; Chandra et al., 1998; Lorra Garey et al., 2015). However, because WHIV change their alcohol use patterns over time (Cook et al., 2013), existing studies may not have captured the full picture. Understanding the relationship between change in anxiety and changes in alcohol use among WHIV may help promote gender-specific interventions that address both anxiety symptoms and alcohol use, ultimately reducing associated adverse outcomes in this population.

Thus, the purpose of this study is to build upon previous literature by examining associations between change in anxiety and changes in alcohol use among WHIV over time. We hypothesized that change in anxiety would be positively associated with changes in alcohol use among WHIV.

METHOD

Study recruitment

This was a longitudinal analysis of data from two concurrently recruited cohorts of WHIV. One was a randomized controlled trial (RCT) designed to test the effectiveness of a brief alcohol

intervention (BI) among 153 WHIV with baseline at-risk drinking (defined as 8 or more drinks/week, 2 or more binge drinking episodes [defined as 4 or more drinks/occasion] in the past six months, or TWEAK score ≥2) who were not currently receiving alcohol treatment (Chander et al., 2015). The TWEAK alcohol screening consists of five-questions with a total score of 7 points; a total score ≥2 indicates at-risk drinking (Russell, 1994). The second cohort was a concurrently recruited sample of 234 WHIV without at-risk drinking at baseline in care at the same clinic (Barai et al., 2016). The parent studies were registered at clinicaltrials.gov: NCT00127231; both studies were approved by the Johns Hopkins Medicine Institutional Review Board.

Participants were recruited between March, 2006 and September, 2010 through several methods, including clinic flyers, provider referral, waiting room recruitment, and review of drinking data obtained from an audio-computer-assisted-self-interview (ACASI) administered every six months to patients who have consented to enroll in the HIV Clinical Cohort (Chander et al., 2015). Two parent studies inclusion criteria included women who 1) had a confirmed HIV infection; 2) received outpatient care at the Johns Hopkins HIV Clinic; 3) were 18 years of age or older; 4) not pregnant; and 5) had no history of psychosis at the time of enrollment. Women in the RCT had visits at baseline and three, six, and twelve months post-enrollment; women in the non-at-risk drinking cohort had visits at baseline, and six, and twelve months post-enrollment. For the purpose of this study, we used data at baseline, six months, and twelve months post-enrollment for both cohorts.

Independent variable: change in anxiety

Anxiety was measured at each visit using the Hospital Anxiety and Depression Scale Anxiety Subscale (HADS-A), which consists of seven questions related to generalized anxiety disorder (GAD) (Zigmond & Snaith, 1983). Each question is scored from 0-3 for a maximum score of 21. HADS-A scores can be grouped into three clinical categories: normal: 0-7, borderline abnormal: 8-10, and abnormal: 11-21 (Zigmond & Snaith, 1983). A systematic review reported that Cronbach's

alpha for HADS-A varied from 0.68 to 0.93 (mean 0.83) (Bjelland, Dahl, Haug, & Neckelmann, 2002). Our independent variable, change in anxiety, was measured as a change in the clinical category of HADS-A score between two serial visits that were 6 months apart. Changes in anxiety were categorized as unchanged anxiety, increased anxiety, and deceased anxiety.

Dependent Variable: changes in alcohol use

In this study, alcohol use was measured using the well-validated 90-day timeline follow back method (TLFB) (Roy et al., 2008; Sobell et al., 2003). Using this retrospective method, the trained interviewer constructed a 90-day calendar that provided daily estimates of the type and amount of alcohol use summarized as standard drinks (Annis et al., 1996). Alcohol use over the most recent 90 days was summarized using three indicators: average number of drinks per drinking day, number of drinking days, and number of binge days ($\geq$ 4 drinks on a single day) in the 90 days preceding each study visit.

Additional covariates of interest

Additional covariates of interest were selected based on previous literature (Samet et al., 2007). Of those covariates, socio-demographic factors included age (continuous variable), cohabitating partner status (currently living with a partner or not), education (years completed, continuous variable), race/ethnicity (self-identified as African-American/Black or others [including Caucasians, Hispanic, Alaskan Native, Asian, American Indian or refused to answer]). Age, race, domestic cohabitating partner status, education, antiretroviral therapy (ART) use (current use or not) were obtained through an Audio Computer Assisted Self Interview (ACASI) at baseline visit. Cocaine use was obtained from the TLFB at each visit. Depression was assessed via ACASI using the Beck Depression Inventory (BDI), which is a 21-item self-report inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). BDI score can be grouped into four clinical categories: 0-9

indicating minimal depression, 10-18 mild depression, 19-29 moderate depression, and 30-63 severe depression. Change in depression was measured as a change in the clinical category of depression between two visits that were 6 months apart and contained three possible levels: increased depression, unchanged depression, and decreased depression. Change in cocaine use was grouped into three possible levels: use to no use, unchanged, and no use to use between two serial visits that were 6 months apart. Finally, we combined ART use and viral load into a single covariate with three possible levels: detectable viral load without ART, detectable viral load with ART, and undetectable viral load with or without ART. Viral load was drawn on the day of the baseline visit if there had been none in the medical record in the 30 days prior to baseline visit.

Analysis

To be included in this analysis, participants were required to 1) have reported at least one drinking episode at one of their visits; 2) have at least two serial study visits that were six months apart; and 3) have complete data on the covariates selected for analysis. Participants not meeting the above criteria were dropped (n=163). To examine the association between change in anxiety and changes in alcohol use, we constructed three mixed-effects models with dependent variables being change in average number of drinks per drinking day, change in number of drinking days, and change in number of binge days over the past 90 days. Our independent variable was change in anxiety. We adjusted all three models for the following time-fixed covariates: age, cohabitating partner status, education, race, and a combined covariate on whether a person is currently taking ART, and whether a person's viral load is detectable. We also adjusted for the time-varying covariates of cocaine use and depression. We used generalized estimation equation to account for repeated measures of the same individual. All Analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, North Carolina).

RESULTS

Sample characteristics

A total of 387 women were recruited into the two cohorts, 153 from RCT and 234 from the observational cohort. During analysis, a total of 163 were excluded including 125 nondrinkers, 7 with missing values, 31 who did not have two serial visits that were six months apart. The final study population consisted of 224 WHIV. There were no differences in socio-demographic characteristics between the included and excluded participants. Among the 224 women, 216 completed all three study visits and were included in the assessments of changes between the baseline and six-month visit, as well as between the six-month and 12-month visit. Eight women participated in two study visits and were included in one assessment of change between either the baseline and six-month visit or the six-month and 12-month visit. Out of the total of 440 intervals, at-risk drinkers contributed 263 study intervals and non-at-risk drinkers contributed 177 study intervals. Characteristics of the study population, stratified by baseline drinking status, were presented in Table 1. The 224 study participants were predominantly African-American, aged around 45 years old, and most completed less than a high school education (<12 years). They reported an average of 14.82 binge days (SD= 24.44), 19.50 drinking days (26.12), and 6.20 drinks (SD=7.27) on a drinking day in the past 90 days at baseline visit. Participants with at-risk drinking at baseline had higher mean BDI depression score ($p=0.047$) and HADS-A anxiety score ($p=0.045$) and were more likely to use cocaine ($p=0.006$). However, there was no difference in the distribution of the depression or anxiety clinical categories between the two baseline drinking groups ($p=0.39$, $p=0.33$).

Change in Anxiety

Among the 263 intervals with at-risk drinking at baseline, anxiety category decreased in 46%, increased in 38%, and remained unchanged in 15%. Among the 177 intervals with non-at-risk

drinking at baseline, anxiety category decreased in 46%, increased in 40%, and remained unchanged in 14% of the intervals.

Change in Alcohol Use

Among the 263 intervals with at-risk drinking at baseline, binge days decreased in 59%, increased in 30%, and remained unchanged in 11% of the intervals (median change of binge days in one interval = -2 days, interquartile range [IQR]: -10.55, 1.82). Average number of drinks per drinking day decreased in 59%, increased in 34%, and remained unchanged in 7% of the intervals (median change of drinks per drinking day in one interval= -0.88 drinks, IQR: - 4.07, 1.03). Drinking days decreased in 58%, increased in 33%, and remained unchanged in 9% of the intervals (median change of drinking days in one interval= -2 days, IQR: -13, 2).

Among the 177 intervals with non-at-risk drinking at baseline, binge days decreased in 5%, increased in 24%, and remained unchanged in 71% of the intervals (median change of binge days in one interval =0 days, IQR: 0, 0). Drinks per drinking day decreased in 34%, increased in 47%, and remained unchanged in 19% of the intervals (median change of drinks per drinking day in one interval=0 drinks, IQR: -0.99, 1.89). Drinking days decreased in 34%, increased in 41%, and remained unchanged in 25% of the intervals (median change of drinking days in one interval =0 days, IQR: -1, 2).

Associations between change in anxiety and change in alcohol use

Binge Drinking Days

Based on multivariable analysis, there was no significant correlation between change in anxiety and change in binge drinking days (Table 2). However, a change in cocaine use from no use to use between two serial visits was associated with an increase of 9.90 binge drinking days over 90

days compared to no change in cocaine use ($p<0.01$). Moreover, if a participant transitioned into a lower depression category(s) between two serial visits, binge drinking days over 90 days decreased by 5.65 days ($p=0.02$).

Drinking Days

Based on multivariable analysis, there was no significant correlation between change in anxiety and change in drinking days (Table 3). A change in cocaine use from no use to use between two serial visits was associated with an increase of 10.81 drinking days over 90 days compared to no change in cocaine use ($p<0.01$). Moreover, if a participant transitioned into a lower depression category(s) between two serial visits, drinking days over 90 days decreased by 5.02 days ($p=0.04$).

Drinks Per Drinking Day

Based on multivariable analysis, there was no significant correlation between change in anxiety and change in average number of drinks per drinking day (Table 4). A change in cocaine use from use to no use between two serial visits, compared to no change in cocaine use, was associated with a decrease of average 2.75 drinks per drinking day over 90 days ($p<0.01$). A change in cocaine use from no use to use between two serial visits, compared to no change in cocaine use, was associated with an increase of average 2.82 drinks per drinking day over 90 days ($p=0.01$).

DISCUSSION

In this sample of 224 WHIV, baseline GAD measured by HADS-A scores were higher among at-risk compared to non-at-risk drinkers. In line with this, the overall prevalence of GAD at baseline was 25%, with a higher proportion of at-risk drinkers experiencing GAD (29%) compared to non-at-risk drinkers (20%). Contrary to our hypothesis, we did not find a significant association between change in GAD and change in granular measures of alcohol use including binge days, drinking days,

and average number of drinks per drinking day. We did find, however, that increase in cocaine use was associated with increased binge days, drinking days, and average number of drinks per drinking day. Decrease in cocaine use was associated with decreased average number of drinks per drinking day. Decreased depression symptoms were associated with decreased binge drinking days and drinking days. These findings suggest that, in this sample of predominantly black WHIV, change in GAD was not associated with change of alcohol use; cocaine use and depressive symptoms play a greater role in drinking changes.

Our finding that baseline anxiety scores were higher in at-risk compared with non-at-risk drinkers is in line with other cross-sectional studies which found that anxiety (anxiety affect, panic, and social anxiety) is positively associated with alcohol use among PHIV (Lorra Garey et al., 2015; M.-K. Kee et al., 2015) as well as in the general population (Kushner, Abrams, & Borchardt, 2000; McCaul, Hutton, Stephens, Xu, & Wand, 2017; Smith et al., 2006). Potential reasons explaining the association between the two include the self-medication hypothesis and cause-consequence hypothesis (Merikangas, Stevens, & Fenton, 1996). According to the self-medication hypothesis, people drink to cope with anxiety, which in turn escalates their alcohol use via negative reinforcement (Quitkin, Rifkin, Kaplan, & Klein, 1972). Based on the cause-consequence hypothesis, anxiety is a consequence of chronic substance use and/or withdrawal syndrome (George, Nutt, Dwyer, & Linnoila, 1990). Importantly, it appears that the relationship between alcohol problems and anxiety varies across different types of anxiety disorders (Brandt et al., 2017; Kushner et al., 2000). For example, results of Catchment Area Survey indicated that alcohol dependence was associated with nearly all types of anxiety disorders except for simple phobia (Himle & Hill, 1991). Thus, much remains unknown about the relationship between different types of anxiety and alcohol use for PHIV, in particular WHIV.

Although we observed the expected cross-sectional differences in GAD as a function of alcohol use at baseline, we did not observe the hypothesized relationship between change in anxiety symptoms and change in alcohol use. Most women in our study had at-risk drinking at baseline (60.3%), which over represented the true prevalence of alcohol use among WHIV. These women may have had problematic anxiety and alcohol use for so long that the relatively short-term relationship between the two issues was obscured by their chronicity. In addition, these women faced other complexities in life including lack of social support and poor economic well-being which may have overwhelmed the short-term relationship between anxiety and alcohol use. Nevertheless, we believe that our study make a unique contribution to the literature given the fact that most existing studies were mostly cross-sectional, did not adopt detailed measures of drinking, and did not evaluate changes (Bing et al., 2001; Chandra et al., 1998; Lorra Garey et al., 2015; Smith et al., 2006) even though people's drinking change over time (Cook et al., 2013) .

Our study yielded some other important findings. Our study found that if a WHIV's depression category decreased between two 6-month apart visits, binge days and drinking days would decrease. This finding was consistent those of previous studies (L. Garey et al., 2015; Havlik et al., 2011; M. K. Kee et al., 2015; L'Akoa R et al., 2013; Sullivan et al., 2011; Sullivan et al., 2008; Emily C. Williams et al., 2014) and suggests that if WHIV have reduced depressive symptoms, they may not only decrease depression-associated outcomes such as medication nonadherence (Magidson, Saal, Nel, Remmert, & Kagee, 2017) and decreased immune functions (Leserman, 2003) but also binge day, drinking days, and their associated outcomes. The mechanisms between depression and alcohol use remains unclear but a meta-study suggested a causal mechanism in which drinking increases the risk of depression by inducing neurophysiological and metabolic changes in a person. Further studies are needed to clarify this link (Boden & Fergusson, 2011).

Moreover, our study found that for all three indicators of alcohol use, change in cocaine use from no use to use was associated with increased alcohol use. Change in cocaine use from use to no use was associated with decreased average number of drinks per drinking day. This finding is supported by several studies where researchers demonstrated that cocaine use was positively associated with alcohol use among PHIV (Chander et al., 2006; Crane et al., 2017) as well as the general population (Pennings, Leccese, & Wolff, 2002). Prior research suggests that people used cocaine and alcohol together to intensify the high feeling of cocaine and to reduce the feeling of drunkenness (Pennings et al., 2002). Among our participants, cocaine use was prevalent (26%), especially among those with at-risk drinking at baseline (33.3%). This finding warrants our attention because of the greater-than-additive effects of cocaine and alcohol taken together. The combined use of alcohol and cocaine can exacerbate the negative biological and behavioral consequences compared to the use of either alone, including cardiotoxicity, violent thoughts, and threats (Pennings et al., 2002). Furthermore, for PHIV, cocaine use is associated with accelerated HIV disease progression, decreased medication adherence, and increased mortality (Baum et al., 2009; Vittinghoff et al., 2001). Of particular interest, our study indicates that among WHIV, for alcohol use and cocaine use, an increase in one may lead to an increase in the other substance. Thus, we should consider targeting both substances when developing substance prevention/reduction interventions. Although alcohol screening and brief interventions have been shown to be effective in reducing drinking for WHIV (Chander et al., 2015) and uninfected women with at-risk drinking (Manwell, Fleming, Mundt, Stauffacher, & Barry, 2000; O'Donnell et al., 2014), our study indicates that it is important to develop integrated alcohol and cocaine prevention/reduction interventions targeting WHIV as increasing cocaine use may lead to not only cocaine-associated outcomes but also increases in alcohol use and alcohol-associated adverse outcomes.

So far as we know, this is the first longitudinal study to examine GAD and alcohol use among WHIV. Research on anxiety targeting PHIV is limited despite of its high importance given the prevalence of the problem and its negative physical and emotional effects on this population (Brandt et al., 2017; Chander et al., 2006). Thus, our study targeted a much-needed area. There are several other strengths to this study including rigorous assessment and granular measures of alcohol use in an urban sample of WHIV. It's important to look at alcohol use using different indicators because their associated health risks may differ. For example, binge drinking is associated with over half of alcohol associated deaths in the general population in the US between 2002-2005 (Kanny et al., 2013). In addition, women are biologically more vulnerable to the negative effects of alcohol use than men and are less likely to receive and more likely to delay alcohol treatment than men (Green et al., 2001). The participants in this study mainly consisted of middle-aged black WHIV, most of whom completed less than high school education, and reported a low income. They are a marginalized group in our society but are overrepresented among WHIV (Duarte, Parada, & Souza Ldo, 2014; L'Akoa R et al., 2013). For WHIV, alcohol use may further contribute to HIV-related health disparities after diagnosis (Myers et al., 2009), negatively affect their use of available HIV prevention and treatment resources (Hader, Smith, Moore, & Holmberg, 2001), and lead to negative social interactions (Myers et al., 2009). However, research studies have understudied WHIV, especially African-American WHIV (DeJong & Battistin, 2015; Myers et al., 2009). Last but not the least, demographic (age, race, employment status, domestic partner status), behavioral (ART use, cocaine use) and psychosocial factors (depression) were controlled in the analysis to yield the independent effects of changes of anxiety on changes of alcohol use.

Despite of the merits mentioned above, this study has some limitations. First, alcohol use was measured by self-reported calendar method. While this method has been demonstrated to be reliable and is widely used (Carpenter, Mayer, Fisher, Desai, & Durand, 1989), participants' self-report may

underestimate their drinking. Indeed, the latest development in biomarkers, such as phosphatidylethanol (PEth) in blood offers a more advanced method to assess the accuracy of self-reported alcohol use (Walther et al., 2015). Future studies can use biomarkers in conjunction with traditional self-report approaches to assess the relationship between anxiety and alcohol use more accurately. Moreover, in this study, we only assessed GAD using HADS-A and thus cannot generalize our findings to other types of anxiety. In addition, in the parent study, WHIV with at-risk drinking were purposefully over-sampled and thus our study population did not reflect the true prevalence of alcohol use among WHIV. Finally, statistically, with limited number of visit we were not able to establish models that infer causality by creating lagging of time. Future longitudinal studies assessing different types of anxiety, containing a more representative sample, using the latest biomarkers to evaluate alcohol use, and having multiple time intervals to assess changes with lagging are warranted.

The implications for clinical practice based on our findings are as follows: Although we did not detect a relationship between change in anxiety and change in alcohol use, we have other relevant findings that demonstrated the risks of cocaine use and depression on alcohol use among WHIV. Clinicians should assess depression status and cocaine use status for WHIV and provide them with resources and strategies to manage their depression and cocaine use. Clinicians should inform WHIV that if they increase cocaine or alcohol, they would possibly increase the use of the other substances and suffer from adverse outcomes associated with both substances.

Table 1. Participants' Baseline Characteristics				
	All participants (n=224)	Non-at-risk drinkers (n=89)	At risk drinkers (n= 135)	P-value
Age (years)[1]	45.79 (8.17)	46.74 (8.76)	45.16 (7.72)	0.17
Education (years)[1]	11.40 (2.08)	11.62 (2.26)	11.26 (1.95)	0.22
African-American[2]	186 (83.0%)	73 (82.0%)	113 (83.7%)	0.74
Living without a partner[2]	196 (87.5%)	76 (85.4%)	120 (88.9%)	0.44
Viral load and ART				0.48
Detectable viral load& no ART[2]	52 (23.2%)	17 (19.1%)	35 (25.9%)	-
Undetectable viral load with /without ART[2]	108 (48.2%)	46 (51.7%)	62 (45.9%)	-
Reference: Detectable viral load & ART[2]	64 (28.6%)	26 (29.2%)	38 (28.1%)	-
Unemployed[2]	189 (84.3%)	73 (80.1%)	116 (85.9%)	0.43
Anxiety (HADS-A total)[1]	7.37 (4.62)	6.58 (5.02)	7.89 (4.28)	**0.045**
Normal anxiety[2]	125 (55.8%)	54 (60.7%)	71 (52.6%))	0.33
Borderline anxiety[2]	42 (18.8%)	17 (19.1%)	25 (18.5%)	
Abnormal anxiety[2]	57 (25.4%)	18 (20.2%)	39 (28.9%)	
Average number of binge days in the past 90 days[1, 3]	14.82 (24.44)	0.00 (0.00)	24.59 (27.42)	**<0.01**
Average number of drinking days in the past 90 days[1]	19.50 (26.12)	2.87 (6.34)	30.45 (28.36)	**<0.01**
Average number of drinks on a drinking day in the past 90 days[1]	6.20 (7.27)	1.06 (1.13)	9.58 (7.63)	**<0.01**
Depression (BDI total)[1]	9.81 (8.80)	8.37 (8.90)	10.76 (8.64)	**0.047**
Minimal depression[2]	127 (56.7%)	56 (25.0%)	71 (31.7%)	0.39
Mild depression[2]	54 (24.1%)	20 (8.9%)	34 (15.2%)	
Moderate depression[2]	38 (17.0%)	11 (4.9%)	27 (12.0%)	
Severe depression[2]	5 (2.2%)	2 (0.9%)	3 (1.3%)	
Use cocaine[2]	60 (26.8%)	15 (16.9%)	45 (33.3%)	**0.006**

1.Numbers indicate mean [SD]. 2. Numbers indicate n [%]. 3. Binge days refer to≥ 4 drinks on a single day.

Table 2. Mixed effect model examining the association between changes in anxiety and changes in average number of binge days among WHIV				
Predictor	Estimate	SE(B)	T Value	Pr>|t|
Intercept	1.75	7.39	0.24	0.81

Age (years)	-0.14	0.11	-1.27	0.21
Domestic partner				
Living with a partner	-0.64	2.69	-0.24	0.81
Reference: no partner	0	-	-	-
Change of cocaine use				
Use to no use	-1.67	3.12	-0.53	0.60
No use to use	9.90	3.38	2.92	**<0.01**
Reference: no change	0	-	-	-
Education (years)	0.24	0.44	0.55	0.58
Race				
African Americans	-1.17	2.44	-0.48	0.63
Reference: other races	0	-	-	
Changes in anxiety category				
Decreased	-2.56	2.38	-1.07	0.28
Increased	3.49	2.55	1.37	0.17
Reference: no change	0	-	-	-
Changes in depression category				
Decreased	-5.65	2.30	-2.46	**0.02**
Increased	1.27	2.80	0.45	0.65
Reference: no change	0	-	-	-
Viral load and ART				
Detectable viral load& no ART[2]	0.15	2.73	0.06	0.96
Undetectable viral load with /without ART[2]	0.38	2.19	0.17	0.86
Reference: detectable viral load & ART[2]	0	-	-	-

Model AICC= 3779.7, P<.0001

Table 3. Mixed effect model examining the association between changes in anxiety and changes in average number of drinking days among WHIV

Predictor	Estimate	SE(B)	T Value	Pr>|t|
Intercept	-0.48	7.93	-0.06	0.95
Age (years)	-0.16	0.12	-1.33	0.18
Domestic partner				
Living with a partner	-1.54	2.89	-0.53	0.60
Reference: no partner	0	-	-	-

Change of cocaine use				
Use to no use	-0.16	3.35	-0.05	0.96
No use to use	10.81	3.63	2.98	**<0.01**
Reference: no change	0	-	-	-
Education (years)	0.55	0.47	1.16	0.25
Race				
African Americans	-1.40	2.62	-0.53	0.59
Reference: other races	0	-	-	-
Changes in anxiety category				
Decreased	-2.20	2.56	-0.86	0.39
Increased	1.27	2.74	0.47	0.64
Reference: no change	0	-	-	-
Changes in depression category				
Decreased	-5.02	2.47	-2.03	**0.04**
Increased	3.71	3.00	1.24	0.22
Reference: no change	0	-	-	-
Viral load and ART				
Detectable viral load& no ART[2]	-0.53	2.93	-0.18	0.86
Undetectable viral load with /without ART[2]	-0.59	2.34	-0.25	0.80
Reference: detectable viral load & ART[2]	0	-	-	-

Model AICC= 3840.5, P<.0001

Table 4. Mixed effect model examining the association between changes in anxiety and changes in average number of drinks per drinking day among WHIV

Predictor	Estimate	SE(B)	T Value	Pr>|t|
Intercept	2.03	2.42	0.84	0.40
Age (years)	-0.02	0.04	-0.44	0.66
Domestic partner				
Living with a partner	0.80	0.88	0.91	0.46
Reference: no partner	0	-	-	-
Change of cocaine use				
Use to no use	-2.75	1.02	-2.69	**<0.01**
No use to use	2.82	1.11	2.54	**0.01**
Reference: no change	0	-	-	-
Education (years)	-0.21	0.14	-1.43	0.16

Race				
African Americans	0.65	0.80	0.81	0.42
Reference: other races	0	-	-	
Changes in anxiety category				
Decreased	-0.76	0.78	-0.97	0.33
Increased	0.68	0.83	0.81	0.42
Reference: no change	0	-	-	-
Changes in depression category				
Decreased	0.85	0.75	-1.13	0.26
Increased	-0.77	0.91	-0.84	0.40
Reference: no change	0	-	-	-
Viral load and ART				
Detectable viral load& no ART[2]	-0.51	0.89	-0.57	0.57
Undetectable viral load with /without ART[2]	0.33	0.72	0.45	0.65
Reference: detectable viral load & ART[2]	0	-	-	-

Model AICC= 2825.4, P<.0001

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Chapter 4: The Relationship between Alcohol Use, Anxiety, and Depression and Retrospective Attendance of Primary Care Visits among Women with Human Immunodeficiency Virus

Abstract

Background: Retention in care (RIC) is important for women with human immunodeficiency virus (WHIV) to achieve desired health outcomes. In this study, we sought to determine the associations between alcohol use, anxiety, and depression and RIC among WHIV.

Methods: Alcohol use was assessed using the Timeline Follow-back; measures included number of standard drinks per drinking days, drinking days, and binge drinking days. Anxiety symptoms were assessed with Hospital Anxiety and Depression, Anxiety Subscale (HADS-A); scores were categorized into three severity levels. Depressive symptoms were assessed with Beck Depression Inventory (BDI); scores were categorized into four severity levels. Primary care visits over the prior twelve months were collected from clinic registration records and classified as "show" or "no show". We used three logistic mixed models, each with a single alcohol use measure (drinks per drinking day, binge drinking days, or drinking days) to examine the associations between alcohol use, anxiety, depression and attendance of primary care visits, adjusting for age, race/ethnicity, education, domestic partner status, viral load, cocaine use, and antiretroviral therapy status (ART).

Results: Among 364 WHIV, mean attendance of primary care visits was 63.9%. Every one-day increase in binge drinking days (Odds ratio [OR]=0.99, 95% CI 0.99,1.00) or drinking days (OR=0.99, 95% CI 0.99, 1.00) was associated with decreased odds of attending primary care visits(p=0.02). Moderate/severe anxiety scores, compared to normal anxiety scores, were associated with decreased odds of attending primary care visits (OR=0.69, 95% CI 0.50, 0.97). Depressive symptoms were not significantly associated with retention in care. In all three models, increasing age and undetectable viral load (compared to detectable viral load) were associated with increased odds

of attending primary care visits. Cocaine use (compared to no use) was associated with decreased odds of attending primary care visits.

Conclusions: Our findings indicate that identifying and treating WHIV with alcohol use especially binge drinking as well as cocaine use and/or moderate/severe anxiety could potentially improve their RIC.

Key words: Women, HIV, anxiety, alcohol, retention in care, cocaine

INTRODUCTION

Engagement and retention in care are associated with suppressed viral load (Robbins et al., 2007; Sethi, Celentano, Gange, Moore, & Gallant, 2003) and decreased likelihood of death (Giordano et al., 2007; Lee et al., 2013; Mugavero et al., 2009) among people with HIV (PHIV), and thus are critical steps in the HIV Care Continuum (Kay, Batey, & Mugavero, 2016). Retention in care (RIC) is defined in different ways and includes attending two medical visits at least 90 days apart (Institute of Medicine [IoM] index and the Department of Health and Human Services [DHHS] indicator (Rebeiro et al., 2014)), missed clinical visits (Mugavero et al., 2014) or both (Horstmann, Brown, Islam, Buck, & Agins, 2010). Although the IoM/DHHS definition often serves as a national benchmark and is required to be reported by certain HIV services agencies (Committee on Review Data Systems for Monitoring HIV Care), if we solely rely on this definition to examine RIC, we may undercount the number of missed visits and their consequences even among persons who are classified as being retained. Prior studies found that missed clinical visits are exceedingly common even among PHIV who are classified as retained and if we further evaluate missed clinic visits among those individuals, we can obtain additional independent prognostic information about them such as risk of all-cause mortality (Mugavero et al., 2014).

In the US, a significant proportion of PHIV have poor RIC (Mugavero, Amico, Horn, & Thompson, 2013; Robbins et al., 2007), even among those attending Veteran Affairs Hospitals or clinics where few financial barriers exist (Giordano et al., 2007). Prevalence of non-RIC in PHIV

varies widely among published studies, ranging from 11% to 42% depending on socio-demographic, behavioral, and health profiles of the study population and approaches to measuring RIC (Giordano et al., 2007; Monroe et al., 2016; Robbins et al., 2007; Yang, Yan, Liu, Huang, & Long, 2015). Poor RIC is associated with socio-cultural, economic, and health factors (Tiruneh, Galarraga, Genberg, & Wilson, 2016). According to a national cohort study of 2,619 US veterans, being black, younger age, high CD4 cell count (>350 cells/μL), and illicit drug use predict poor RIC (Giordano, Hartman, Gifford, Backus, & Morgan, 2009). In addition, in qualitative work, researchers identified fear of stigma, care dissatisfaction, and economic constraints to be factors that impeded RIC among PHIV (Tiruneh et al., 2016).

At-risk drinking is another concern for PHIV. For the general population, it is defined as drinking on average >2 standard drinks (one drink contains 14 grams of pure alcohol) per day for men, and >1 drink per day for women (Alcoholism, 2016). For PHIV, they may face increased risk of developing adverse outcomes even at lower levels of consumption (Bonacini, 2011). Numerous studies demonstrate an association between alcohol use and medication nonadherence (Beer & Skarbinski, 2014; Braithwaite et al., 2005; Carrico, Woolf-King, Neilands, Dilworth, & Johnson, 2014; Chitsaz et al., 2013; Conen et al., 2009; Herrmann et al., 2012; Holmes, Bilker, Wang, Chapman, & Gross, 2007; Lima et al., 2014; Marks King et al., 2012; Ohl et al., 2013; Parsons, Rosof, & Mustanski, 2008; Williams et al., 2014; Woolf-King, Neilands, Dilworth, Carrico, & Johnson, 2014) and delayed treatment initiation (Koirala et al., 2017) among PHIV. However, fewer studies have examined the association between alcohol use on and attendance of primary care visits, particularly among women with HIV (WHIV) (Koirala et al., 2017; Mugavero et al., 2013). It is especially important to look at this issue among WHIV because 1) drinking is more prevalent among WHIV than women not with HIV (Neblett et al., 2011); 2) women compared with men are less likely to disclose drinking to primary care providers (Cucciare et al., 2016); 3) women are more vulnerable to the effects of alcohol than men due to decreased first-pass metabolism of alcohol and a lower

proportion of water in their body (Cole-Harding & Wilson, 1987; Frezza et al., 1990); and 4) women are more likely to delay treatment for alcohol use disorder compared with men (Green, Freeborn, & Polen, 2001).

Another issue that needs to be specially attended to in WHIV is mental health symptoms such as anxiety and depression which are more prevalent among women compared with men in the general population and among PHIV (Chander & McCaul, 2003; McLean, Asnaani, Litz, & Hofmann, 2011; Saadat, Behboodi, & Saadat, 2015; van den Heuvel et al., 2013). These symptoms may negatively affect HIV-related outcomes in this population (Chander, Himelhoch, & Moore, 2006). Although there is extensive literature demonstrating the negative relationship between mental health symptoms and medication adherence (Magidson, Saal, Nel, Remmert, & Kagee, 2017), there have been fewer studies examining the relationship between mental health symptoms and attendance of primary care visits among PHIV, even fewer that exclusively targeted WHIV (Zuniga, Yoo-Jeong, Dai, Guo, & Waldrop-Valverde, 2016).

Understanding the association between alcohol use and mental health symptoms and attendance of primary care visits among WHIV is important given the impact of those issues on health outcomes of WHIV. Thus, the purpose of this study was to build upon previous literature by examining the relationships between alcohol use, anxiety, and depression, and likelihood of attending primary care visits among WLHV. We hypothesized that the factors above would be negatively associated with attendance of primary care visits among WHIV.

METHODS

Study recruitment

Data used in this study came from two concurrently recruited cohorts of WHIV. One was a randomized controlled trial (RCT) designed to test the effectiveness of a brief alcohol intervention (BI) among 153 WHIV with baseline at-risk drinking (defined as 8 or more drinks/week, 2 or more binge drinking episodes [defined as 4 or more drinks/occasion] in the past six months, or TWEAK

score ≥2) who were not currently receiving alcohol treatment (Chander, Hutton, Lau, Xu, & McCaul, 2015). The TWEAK alcohol screening consists of five-questions with a total score of 7 points; a total score ≥2 indicates at-risk drinking (Russell, 1994). The second cohort was a concurrently recruited sample of 234 WHIV without at-risk drinking at baseline in care at the same clinic (Barai et al., 2016). The parent studies were registered at clinicaltrials.gov: NCT00127231; both studies were approved by the Johns Hopkins Medicine Institutional Review Board.

Participants were recruited between March, 2006 and September, 2010 through clinic flyers, provider referral, waiting room recruitment, and review of drinking data obtained from an audio-computer-assisted-self-interview (ACASI) routinely administered to patients enrolled in the HIV Clinical Cohort every six months (Chander et al., 2015). Study inclusion criteria included women who 1) had a confirmed HIV infection; 2) received outpatient care at the Johns Hopkins HIV Clinic; 3) were 18 years of age or older; 4) were not receiving treatment for an alcohol use disorder (AUD); 5) were not pregnant; and 6) had no history of psychosis at the time of enrollment.

Independent variable: Alcohol use at baseline

In this study, alcohol use was measured using the well-validated 90-day timeline follow back (TLFB) (Roy et al., 2008; Sobell et al., 2003) at participants' baseline visit. Using this retrospective method, the trained interviewer constructed a 90-day calendar that provided daily estimates of the type and amount of drinking which were summarized as standard drinks (Annis et al., 1996). Alcohol use was then converted into three measures, including average number of drinks per drinking day, number of drinking days, and number of binge days in the past 90 days preceding a participant's baseline visit.

Independent variable: Anxiety and depression at baseline

Anxiety was measured using the Hospital Anxiety and Depression Scale Anxiety Subscale (HADS-A), which consists of seven questions related to generalized anxiety disorder (GAD) (Zigmond & Snaith, 1983) with a maximum score of 21. HADS-A scores would then be grouped into three clinical categories: normal (0-7), mild (8-10), and moderate/severe (11-21) (Zigmond & Snaith, 1983). A systematic review reported that Cronbach's alpha for HADS-A varied between 0.68 and 0.93 (mean 0.83) (Bjelland, Dahl, Haug, & Neckelmann, 2002). Depression was measured using the Beck Depression Inventory (BDI), which is a 21-item self-report inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) with a maximum score of 63. BDI total score was then categorized into four clinical depression categories: minimal (0-9), mild (10-18), moderate (19-29), and severe (30-63).

Dependent variable: Attendance of primary care visits over 12 months prior to baseline

In this study, we used clinic registration data to capture primary care visit attendance over the 12 months prior to participants' baseline study visit. Visits were classified as "show", "no show" or "cancelled". Cancelled visits were excluded from this analysis, and our outcome was operationalized as a binary variable ("show" or "no show").

Additional covariates of interest

Additional covariates included age (continuous variable), education (years completed, continuous variable), cohabitating partner status (currently living with a partner or not), race/ethnicity (self-identified as African-American/Black or others [including Caucasians, Hispanic, Alaskan Native, Asian, American Indian or refused to answer]), and whether a person used cocaine (yes or no). We combined use of antiretroviral therapy (ART) and viral load into a single covariate with three nominal levels (detectable viral load without ART, undetectable viral load with/without ART, and detectable viral load with ART). Race, domestic cohabitating partner status, ART use, and education were obtained through ACASI at baseline visit. Cocaine use was obtained using the 90-day

TLFB at baseline visit. Viral load was drawn on the day of the baseline visit if there had been none in the medical record in the 30 days prior to baseline visit.

Statistical analysis

To be included in this analysis, participants were required to have complete data on the variables selected for analysis. Participants not meeting the above criteria were dropped (N=23). To examine the association of baseline alcohol use, anxiety, and depression on attendance of primary care visits over prior 12 months, we constructed three logistic mixed models, with independent variables being 1) average number of drinks per drinking day, 2) number of drinking days, and 3) number of binge days over the past 90 days prior to baseline visit respectively. Our dependent variable primary care visit attendance was operationalized as a binary distributed outcome ("1" for show and "0" for no show). Only visits within 365 days prior to baseline were included into analysis. Depressive and anxiety symptoms were included in all the three models. We adjusted the three models for the following time-fixed covariates: age, cohabitating partner status, education, race, and a combined covariate on ART and viral load detectable, and whether a person used cocaine. We used generalized estimation equation to account for repeated visits of the same individuals. All Analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, North Carolina).

RESULTS

Sample characteristics

A total of 387 women were recruited into the two cohorts, 153 from RCT and 234 from the observational cohort. During analysis, 23 were excluded due to missing information. The final study population consisted of 364 WHIV. There were no socio-demographic differences between the included and excluded participants. Characteristics of the study population are presented in Table 1. Participants were predominantly African-American, age around 46 years old, had an average

education of 11.44 years, and were living without a partner (87.6%). Twenty two percent of them used cocaine and 23.6% of them had moderate-to-severe levels of anxiety. They reported an average of 10.25 binge days, 13.35 drinking days, and 4.43 drinks on a drinking day in the past 90 days preceding baseline visit. On average, they had 8.47 scheduled visits over 12 months and attended 63.9% of them.

Associations between alcohol use, anxiety, and depression and attendance of primary care visits

Drinks per drinking day

In multivariable analysis, there were no significant relationships between drinks per drinking day and depression symptoms and attendance of primary care visits (Table 2, Model 1). However, moderate/severe anxiety, compared to normal anxiety, was associated with decreased odds of attending primary care visits (Odds ratio [OR]=0.69, 95% CI 0.50,0.97). Every one-year increase in age was associated with increased odds of attending primary care visits (OR=1.02, 95% CI 1.01, 1.04). Undetectable viral load, compared to detectable viral load, was associated with increased odds of attending primary care visits (OR=1.64, 95% CI 1.20, 2.26). Cocaine use, compared to no use, was associated with decreased odds of attending primary care visits (OR=0.57, 95% CI 0.43, 0.75)

Binge drinking days

In multivariable analysis, every one-day increase in binge drinking days was associated with decreased odds of attending primary care visits (OR=0.99, 95% CI 0.99, 1.00) (Table 2, Model 2). Moderate/severe anxiety, compared to normal anxiety, was associated with decreased odds of attending primary care visits (OR=0.69, 95% CI 0.49, 0.96). Depression was not associated with odds of attending primary care visits. Moreover, every one-year increase in age was associated with increased odds of attending primary care visits (OR=1.02, 95% CI 1.01-1.04). Undetectable viral load, compared to detectable viral load, was associated with increased odds of attending primary care

visits (OR=1.61, 95% CI 1.17, 2.21). Cocaine use, compared to no use, was associated with decreased odds of attending primary care visits (OR=0.57, 95% CI 0.43, 0.75).

Drinking days

In multivariable analysis, every one-day increase in drinking days was associated with decreased odds of attending primary care visits (OR=0.99, 95% CI 0.99, 1.00) (Table 2, Model 3). Moderate/severe anxiety, compared to normal anxiety was associated with decreased odds of attending primary care visits (OR=0.69, 95% CI 0.50, 0.96). Depression was not associated with odds of attending primary care visits. Moreover, every one-year increase in age was associated with increased odds of attending primary care visits (OR=1.02, 95% CI 1.01-1.04). Undetectable viral load, compared to detectable viral load, was associated with increased odds of attending primary care visits (OR=1.59, 95% CI 1.15, 2.18). Cocaine use, compared to no use, was associated with decreased odds of attending primary care visits (OR=0.57, 95% CI 0.43, 0.75).

DISCUSSION

In this sample of 364 WHIV, drinking days and binge drinking days were each associated with a reduction in primary care visit attendance after adjusting for age, race/ethnicity, education, domestic partner status, viral load, ART, depression, anxiety, and cocaine use. Moderate/severe anxiety and cocaine use were also independently associated with a reduction in visit attendance, irrespective of quantity or frequency of alcohol use. Depression, however, was not significantly associated with visit attendance in any model. These findings suggest that in this sample of predominantly middle-aged African American WHIV, frequency of alcohol use (binge drinking days and drinking days), age, cocaine use, and moderate/severe anxiety play a role in their RIC. Since RIC plays a key role in the HIV care continuum and ultimately affects PHIV's health outcomes, the above

modifiable factors (alcohol use, cocaine use, and moderate/severe anxiety) that are negatively associated with RIC should be targeted for screening and treatment in the clinical setting.

Our study found that among WHIV, frequency of alcohol use is negatively associated with RIC. This finding is consistent with prior studies with mixed samples of both men and women with HIV across various measures of RIC and alcohol use (Giordano et al., 2009; Giordano et al., 2005; Koirala et al., 2017; Monroe et al., 2016). In a study of 9,694 PHIV, heavy alcohol use was associated with worse IOM-defined retention, and daily/weekly binge drinking was associated with lower visit adherence (kept visits/ scheduled+ kept visits) (Monroe et al., 2016). Other studies of PHIV have used other measures to assess RIC such as at least one HIV care visit over 12 months (Koirala et al., 2017), and ≤6 months' gap in care in the initial period (Giordano et al., 2005) and got consistent findings as our study. Importantly, our study not only reinforces findings of prior literature but also extends them to a sample of urban WHIV. Furthermore, in our study, we assessed RIC using missed visits rather than number of attended visits at defined intervals (or visit constancy) because the former could provide more prognostic information about a person's health such as trend of change in CD4 count and plasma HIV level (Walburn, Swindells, Fisher, High, & Islam, 2012) and long-term mortality (Horberg et al., 2013; Mugavero et al., 2009) regardless of their retaining status defined by the IOM index and the DHHS indicator.

Our study also finds that moderate/severe anxiety is negatively associated with RIC among WHIV. To date, there have been relatively few studies examining the effects of anxiety on RIC. In a qualitative study, researchers identified anxiety to be a barrier for PHIV to attend primary care visits (Tiruneh et al., 2016). This may relate to the fact that individuals with moderate/severe anxiety exhibit high levels of emotional, cognitive, and behavioral efforts to avoid or escape sources of distress (Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). Those WHIV with moderate/severe anxiety may try to escape HIV-related events and thus were more likely to miss HIV primary care visits compared to those without moderate/severe anxiety. However, in another study of 136 PHIV in

South Africa, researchers found that anxiety is not associated with loss from care (not attending an appointment or receiving medications for three or more months or medical files removed) (Cichowitz, Maraba, Hamilton, Charalambous, & Hoffmann, 2017). However, in that study, researchers used a cut-off of 8 in the HADS-A score to define anxiety. Including mild cases as having anxiety may have washed out any effect. In addition, participants in that study consist of half men and women with HIV and measured RIC differently than our study.

In addition, our study found that age is positively associated with RIC among this group of WHIV. This is consistent with previous research findings that advanced age is associated with better ART adherence among PHIV (Ettenhofer et al., 2009; Hinkin et al., 2004; Johnson, Heckman, Hansen, Kochman, & Sikkema, 2009; Newman et al., 2012). Our most robust finding that cocaine is negatively associated with RIC is consistent with findings of prior studies (Giordano et al., 2009; Hessol et al., 2009). The underlying mechanism may be that cocaine increases circulating dopamine levels in brain which controls pleasure and movement (National Institute on Drug Abuse) and thus lead to people's behavioral changes such as mood swings, irritability, and paranoia (American Addiction Centers). This high level of disorganization makes WHIV less likely to attend scheduled primary care visits. In addition, we found that undetectable viral load was negatively associated with RIC. This is expected given the fact that undetectable viral load is a marker of good medication adherence (Haubrich et al., 1999; Kalichman et al., 2008) and thus satisfying RIC.

Although some studies found that depressive symptoms are negatively associated with RIC (Cichowitz et al., 2017; Zuniga et al., 2016), our study did not find a significant association. This difference may be secondary to differences in definitions of retention [43] and sample characteristics [57], In addition, in contrast to other studies, we were able to adjust for anxiety symptoms and cocaine use, both of which are associated with depressive symptoms and RIC and may be unmeasured confounders in prior work of RIC. In a study of 433 newly diagnosed pregnant WHIV, researchers found that depression was not a predictor of lost to follow up in HIV care (Yotebieng,

Fokong, & Yotebieng, 2017). Further studies are needed to clarify this between depressive symptoms and RIC among WHIV, adjusting for potential confounders and using prospective methods.

Although there is extensive literature demonstrating the negative relationship between alcohol use, mental health symptoms, and medication adherence (Magidson et al., 2017), there have been fewer studies examining RIC among PHIV, especially WHIV (Zuniga et al., 2016). Since RIC plays a key role in the HIV care continuum and ultimately affects patients' outcomes, our study targeted a much-needed area. Our study yielded more in-depth evidence on the negative relationship between alcohol use and RIC by examining alcohol use with granular measures of use. It is important to look at alcohol use using different measures because their associated health risks often differ. For example, binge drinking is particularly harmful and is associated with over half of alcohol associated deaths in the US between 2002-2005 (Kanny et al., 2013).

Another strength of our study is that the participants mainly consisted of middle-aged African American WHIV, most of whom completed a less than high school education, reported a low income, and lived alone. They are vulnerable in the context of living with HIV. A prior study found that African American WHIV experienced high levels of stigma and marginalization in health care that hindered their RIC (Sangaramoorthy, Jamison, & Dyer, 2017). In addition, for WHIV, alcohol use may further contribute to HIV-related health disparities after diagnosis (Myers et al., 2009), negatively affect their use of available HIV prevention and treatment resources (Hader, Smith, Moore, & Holmberg, 2001), and lead to negative social interactions (Myers et al., 2009).

Despite the merits mentioned above, this study has some limitations. First, alcohol use was measured by self-reported timeline follow back method. While this method has been demonstrated to be reliable and widely used (Carpenter, Mayer, Fisher, Desai, & Durand, 1989), participants' self-report may underestimate their drinking. Indeed, the latest development in biomarkers, such as phosphatidylethanol (PEth) in blood, offers a more advanced method to assess the accuracy of self-reported alcohol use (Monroe et al., 2016). Future studies using biomarkers in conjunction with

traditional self-report approaches may overcome measurement issues related to self-report. Moreover, in this study, we assessed baseline alcohol use using a 90-day TLFB and used retrospective clinical attendance for primary care visits. It is possible that this baseline alcohol use was not reflective of use over the prior 12 months. Future longitudinal prospective studies assessing this relationship are warranted. In addition, participants came from two parent studies, one being an RCT for a brief alcohol intervention. Thus, it is possible that WHIV who enrolled in the RCT were different from general WHIV and had more motivation to attend clinical visits. However, we have, to some extent, overcome this concern by only using retrospective visit data prior to their enrollment in the study.

In summary, in this sample of WHIV, drinking days, binge drinking days, moderate/severe anxiety, and cocaine use were all negatively associated with primary care attendance. Given that missed appointments are associated with poor HIV treatment outcomes, it is important to identify these risk factors for missed appointments and provide resources and treatment that may improve their appointment adherence and HIV treatment outcomes.

Table 1

Characteristics of Study Population

Variables	Study population (n= 364)
Age, years, mean (SD)	46.12 (8.11)
African-American, n (%)	311 (85.4%)
Education, mean (SD)	11.44 (2.03)
Viral load and ART, n (%)	
Detectable viral load& no ART	71 (19.5%)
Undetectable viral load regardless of ART	198 (54.4%)
Detectable viral load & ART	95 (26.1%)
Living without a partner, n (%)	319 (87.6%)
Depressive symptoms, n (%)	
Minimal depression	268 (73.6%)
Mild depression	46 (12.6%)
Moderate depression	41 (11.3%)
Severe depression	9 (2.5%)
Anxiety, n (%)	
Normal	222 (61.0%)
Mild	58 (15.9%)
Moderate/Severe	86 (23.6%)
CD4 Cell Count (cells/mm3), mean (SD)	472.5 (309.1)
Number of binge days, mean (SD)	10.25 (21.20)
Number of drinking days, mean (SD)	13.35 (23.00)
Number of drinks per drinking day, mean (SD)	4.43 (6.81)
Use cocaine vs no use, n (%)	82 (22.5%)
Number of scheduled visits, mean (SD)	8.47 (5.16)
Number of attended visits, mean (SD)	5.41 (3.56)

Note: SD=standard deviation.

Table 2 *Logistic Mixed Models between drinks per drinking day (Model 1), binge drinking days (Model 2), and drinking days (Model 3), and primary care visits attendance*

	Model 1 (drinks per drinking day)		Model 2 (binge drinking days)		Model 3 (drinking days)	
Variables	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.02 (1.01-1.04)	**0.01**	1.02 (1.01--1.04)	**<.01**	1.02 (1.01-1.04)	**0.01**
African-American vs. others	1.05 (0.75-1.46)	0.80	1.04 (0.74-1.45)	0.83	1.05 (0.75-1.46)	0.78
Education	1.02 (0.97-1.09)	0.42	1.02 (0.96-1.08)	0.48	1.02 (0.96-1.08)	0.46
Viral load and ART						
Undetectable viral load	1.64 (1.20-2.26)	**<.01**	1.61 (1.17-2.21)	**<.01**	1.59 (1.15-2.18)	**<.01**
Detectable viral load& no ART	1.26 (0.89-1.77)	0.19	1.24 (0.88-1.74)	0.22	1.22 (0.87-1.71)	0.26
Detectable viral load & ART	Reference	-	Reference	-	Reference	-
Living with a partner vs. without a partner	1.03 (0.73-1.46)	0.87	1.07 (0.76-1.51)	0.71	1.07 (0.76-1.51)	0.71
Depressive symptoms						
Minimal depression	Reference	-	Reference	-	Reference	-
Mild depression	1.41 (0.98-2.05)	0.07	1.42 (0.98-2.05)	0.06	1.42 (0.98-2.05)	0.06
Moderate depression	1.43 (0.95-2.16)	0.08	1.49 (0.99-2.24)	0.06	1.50 (1.00-2.26)	0.05
Severe depression	1.24 (0.53-2.90)	0.62	1.27 (0.55-2.98)	0.58	1.25 (0.54-2.92)	0.60
Anxiety						
Normal	Reference	-	Reference	-	Reference	-
Mild	0.83 (0.60-1.15)	0.27	0.84 (0.61-1.16)	0.29	0.84 (0.61-1.16)	0.30
Moderate/Severe	0.69 (0.50-0.97)	**0.03**	0.69 (0.49-0.96)	**0.03**	0.69 (0.50-0.96)	**0.03**
Number of binge drinking days	-	-	0.99 (0.99-1.00)	**0.02**	-	-
Number of drinking days	-	-	-	-	0.99 (0.99-1.00)	**0.02**
Number of drinks per drinking day	0.99 (0.97-1.00)	0.08	-	-	-	-
Use cocaine vs. no use	0.57 (0.43-0.75)	**<.0001**	0.57 (0.43-0.75)	**<.0001**	0.57 (0.43-0.75)	**<.0001**

Note: OR=Odds ratio, CI=confidence interval, SE=standard error. All analyses were conducted at a 0.05 significance level. Adjusted for age, education, domestic partner status, cocaine use, race/ethnicity, anxiety, viral load, and ART

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Chapter 5: Summary and Conclusions

Although we did not detect a relationship between change in anxiety and changes in alcohol use, we have other relevant findings that demonstrated the risks of cocaine use and depression on alcohol use among WHIV. Clinicians should assess depression status and cocaine use status for WHIV and provide them with resources and strategies to manage their depression and cocaine use. Clinicians should inform WHIV that if they increase cocaine or alcohol, they would possibly increase the use of the other substances and suffer from adverse outcomes associated with both substances.

In addition, we found that drinking days, binge drinking days, moderate/severe anxiety, and cocaine use were all negatively associated with primary care attendance. Given that missed appointments are associated with poor HIV treatment outcomes, it is important to identify these risk factors for missed appointments and provide resources and treatment that may improve their appointment adherence and HIV treatment outcomes.

Biography

Song Ge received her BSN with academic honors from Emory University in 2013, obtained her Registered Nurse license in 2013, and anticipates completing her PhD in nursing from Johns Hopkins University in May 2018. During her PhD study, Song Ge served as visiting instructor at Towson University Department of Nursing in 2016 and as a research and teaching assistant at Johns Hopkins School of Nursing between 2014 and 2018. Her research primarily focuses on mental health symptoms and substance use issues among women living with human immunodeficiency virus. She is an invited reviewer of *Substance Abuse Journal* and *International Journal of Nursing Sciences*. Song Ge also collaborated with faculty members from University of Arkansas and University of Georgia Athens to produce research publications. Song Ge was inducted into the Sigma Theta Tau International Nursing Honor Society in 2012. Song Ge has published four manuscripts in peer-reviewed journals and has six under revision.

CURRICULUM VITA

PERSONAL DATA

Song Ge, BSN, RN
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Baltimore, Maryland 21205
Tel: 678-709-2060
E-mail: sge3@jhu.edu

EDUCATION AND TRAINING

Year	Degree	Institution	Location
2014- Current	PhD Candidate	Johns Hopkins School of Nursing	Baltimore, Maryland
2013	BSN	Emory University School of Nursing	Atlanta, Georgia

CURRENT LICENSE AND CERTIFICATION

Year	Source	Type
2015-present	Maryland Board of Nursing	Registered Nurse
2013-present	Georgia Board of Nursing	Registered Nurse
2015-present	American Heart Association	CPR for Healthcare Providers
2013	Emory University School of Medicine	Fundamentals of Critical Care Support Certificate

PROFESSIONAL EXPERIENCE

Years	Position	Institution	Location
2016	Instructor	Towson University Department of Nursing	Towson, Maryland
2016	School Assistant	Johns Hopkins School of Nursing	Baltimore, Maryland
2015&2016	Research Assistant	Johns Hopkins University	Baltimore, Maryland

2013-2014 Nurse Shandong Province Hospital Jinan, China

HONORS AND AWARDS

2018	Tuition Grant of $500, Johns Hopkins University School of Nursing
2014	Pre-doctoral Award of $28,000, Johns Hopkins University School of Nursing
2015	American Holistic Nurses Association Conference Scholarship of $1100, Johns Hopkins University School of Nursing
2013	Cum Laude for academic excellence, Emory University School of Nursing
2012&2013	Academic Scholarship of $3,000, Emory University School of Nursing
2012	Sigma Theta Tau, The National Nursing Honor Society (inducted member)

RESEARCH

Project: The impact of alcohol use on mental health symptoms and retention in care in women with human immunodeficiency virus (WHIV)

Role: Conducted data cleaning, data analysis, and writing manuscripts
Parent study consist of a randomized controlled trial (RCT) that was used to test the effectiveness of brief alcohol intervention among hazardously drinking WLHIV and a concurrently recruited cohort of non-hazardously drinking WHIV from the same clinic. This study was registered at clinicaltrials.gov: NCT00127231 and received Institutional review board (IRB) approval from the Johns Hopkins School of Medicine IRB. PI: Mary E. McCaul, Johns Hopkins University School of Medicine

Project: The relationship between alcohol use and smoking on health outcomes among middle-aged adults in China

Role: Conducted data cleaning, data analysis, and writing manuscripts
Data came from the China Health and Retirement Longitudinal Study (CHARLS). The CHARLS aims to collect high quality nationally representative sample of Chinese residents ages 45 and older to obtain data regarding the dynamics of retirement and how it interacts with health, health insurance, and economic well-being. The CHARLS provides comprehensive and detailed information on a wide range of domains such as demographics, health status, physical performance, employment history, pension insurance, retirement, income, expenditures, and assets.

Project: A systematic review of eHealth literacy in people living with human immunodeficiency virus.
Role: Conducted literature search, selected articles, conducted quality assessment, and performed data extraction.

SCHOLORSHIP

Journal Articles

Peer-Reviewed (*) indicates data-based

*1. **Ge, S**., al., The Effects of Dietary Calcium Supplements Alone or With Vitamin D on Cholesterol Metabolism: A Meta-Analysis of Randomized Controlled Trials. Journal of Cardiovascular Nursing, 2017. 32(5): p. 496-506.

*2. Luo, X., Liu, T., Yuan, X., **Ge, S.,** Yang J., Li, C., Sun, W. (2015). Factors influencing self-management in Chinese adults with type 2 diabetes: A systematic review and meta-analysis. Health Care and Diabetes. 12, 11304-11327.

3. **Ge, S**, et al., A systematic review of the impact of master's-educated nurses on inpatient care, International Journal of Nursing Sciences (2015), http://dx.doi.org/10.1016/j.ijnss.2015.10.003

4. **Ge, S** et al. Is alcohol use associated with increased risk of developing adverse health outcomes among adults living with human immunodeficiency virus: a systematic review. Journals of Addictions Nursing. *Accepted for publication.*

5. Liu T, **Ge, S** et al. Validating the information-motivation-behavioral skills model of diabetes self-management among Chinese adults with type 2 diabetes: A longitudinal study. BMJ Open. *Under revision.*

6. Han H, Hong H, Starbird L, **Ge, S** et al. A systematic review of eHealth literacy in people living with human immunodeficiency virus. Journal of Medical Internet Research. *Under revision.*

*7. Liu T, **Ge, S** et al. Functional status and cognitive functioning among individuals with diabetes: Findings from the China Health and Retirement Longitudinal Study Baseline Survey. Nursing Research. *Under revision.*

Manuscripts under preparation to submit

*8. **Ge, S** et al. The association between changes in anxiety and changes in alcohol use among women with human immunodeficiency virus. *In preparation to submit to Alcoholism, Clinical, and Experimental Research.*

*9. **Ge, S** et al. The relationship between alcohol use, anxiety, and depression and retrospective attendance of primary care visits among women with human immunodeficiency virus. *In preparation to submit.*

*10. **Ge, S** et al. The relationship between alcohol use and cognitive functioning among middle aged and older adults in China: Findings from the China Health and Retirement Longitudinal Study Baseline Survey. *In preparation to submit.*

*11. **Ge, S** et al. The relationship between smoking and cognitive functioning among middle aged men in China. *In preparation to submit.*

*12. Liu T, **Ge, S** et al. Predictors of depressive symptoms among mid-aged and older men with diabetes in China: An analysis using the China Health and Retirement Longitudinal Study. *In preparation to submit.*

Conference Meetings/Presentations

2017 **Song, G**. (June, 2017). The relationship between changes in alcohol use and changes in anxiety among women living with human immunodeficiency virus. Presented at the International nursing conference, Jinan, China. Presentation, peer-reviewed

2015 **Song, G.**, Sanchez, M., & Finnell, D.S. (July 22, 23, 2015). The potential impact of Master's prepared nurses on patient care in the inpatient setting: A literature review. Presented at the International Network for Doctoral Education in Nursing (INDEN) Biennial Conference, San Juan, Puerto Rico, Poster and paper presentation, peer-reviewed

2016 **Song, G.** (December 20, 21, 2016). The association between changes of anxiety and changes of alcohol use among women living with human immunodeficiency virus. Presented at the International Nursing Research Forum at Wuhan University of Science and Technology, China. Presentation, peer-reviewed

2015 **Song, G.**, Sanchez, M., & Finnell, D.S. (July 22, 23, 2015). The potential impact of master's prepared nurses on patient care in the inpatient setting: A literature review. Presented at the International Network for Doctoral Education in Nursing (INDEN) Biennial Conference, San Juan, Puerto Rico, Poster and presentation, peer-reviewed

EDITORIAL ACTIVITIES

Reviewer of Substance Abuse

Reviewer of Journal of Transplant

Review of International Journal of Nursing Sciences

PROFESSIONAL ACTIVITIES

Member of Sigma Theta Tau, The National Nursing Honor Society

Invited editor and translator of Gerontology nursing textbook (Chinese version)

CURRICULUM VITA

Part II

EDUCATIONAL ACTIVITIES

Towson University, Department of Nursing, Towson, Maryland

Semester/Yr	Course Name	Role	% Effort	Level	#Students
Summer 2016	Nursing Research	Instructor	100%	BSN	19

Johns Hopkins School of Nursing, Baltimore, Maryland

Semester/Yr	Course Name	Role	% Effort	Level	#Students
Spring 2018	Philosophical, theoretical and ethical basis of advanced nursing practice	Teaching Assistant	30%	DNP	37
Fall 2017	Biostatistics for Evidence-Based Practice (online)	Teaching Assistant	50%	DNP	67
Summer 2017	Biostatistics for Evidence-Based Practice	Teaching Assistant	30%	BSN	46
Spring 2017	Biostatistics for Evidence-Based Practice	Teaching Assistant	30%	BSN	60
Fall 2016	Anatomy with Lab	Teaching Assistant	25%	BSN	35
Fall 2016	Leadership for Population Health Management	Teaching Assistant	25%	BSN	40
Summer 2016	Promoting Health in Older Adults	Teaching Assistant	25%	BSN	25
Spring 2016	Biostatistics for Evidence-Based	Teaching	25%	BSN	60

	Practice	Assistant			
Fall 2015	Foundation of Nursing Practice	Teaching Assistant	25%	BSN	60
Spring 2015	Human Growth and Development through the Lifespan (online)	Teaching Assistant	25%	Pre-nursing	25
Spring 2015	Statistical Literacy and Reasoning in Nursing Research (online)	Teaching Assistant	25%	BSN	53