DRINKING, MENTAL HEALTH AND HIV OUTCOMES AMONG PEOPLE WITH HIV AND HAZARDOUS ALCOHOL USE IN VIETNAM

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ABSTRACT

Xuan Binh Minh Nguyen: Drinking, Mental Health and HIV Outcomes Among People Living with HIV and Hazardous Alcohol Use in Vietnam
(Under the direction of Vivian F. Go)

Background: Mental health disorders are the number one comorbidity among people with HIV (PWH). Alcohol use disorders are also very common among this group, with almost half of PWH classified as hazardous drinkers. However, research on the interrelationship between alcohol use, mental health disorders and their effects on HIV outcomes among PWH with hazardous alcohol use remains scarce.

Methods: I conducted three studies using data from a randomized controlled trial in Thai Nguyen, Vietnam, which aimed to evaluate the effects of a combined intervention and a brief intervention drawing from Motivational Enhancement Therapy and Cognitive Behavioral Therapy on alcohol use and viral suppression among antiretroviral therapy (ART) clients with hazardous alcohol use. In study 1, I evaluated the longitudinal associations between mental health symptoms (depression and anxiety symptoms) and two HIV outcomes (viral suppression and complete ART adherence) among participants, and determined whether alcohol dependence modified these associations. In study 2, I described the changes in depression and anxiety symptoms of participants over time and assessed the impact of the combined and brief interventions on depression and anxiety symptoms, comparing the effects of these interventions to each other and to the standard of care (SOC) group. Finally, in study 3, I examined whether alcohol use mediated the pathway from the interventions to depression and anxiety symptoms of participants.

Results: In study 1, depression and anxiety symptoms were associated with a lower probability of complete ART adherence, although they had no overall effect on viral suppression. Alcohol dependence was a significant effect modifier, such that the negative effects of anxiety symptoms on ART adherence were stronger among participants with alcohol dependence, compared to those without. In study 2, depression and anxiety symptoms were common at baseline, and decreases in depression and anxiety symptoms were observed in all three arms over time. There were no significant differences in depression and anxiety symptoms among participants receiving either intervention, relative to the SOC. In study 3, alcohol use, measured as percentage of days abstinent from alcohol in the last 30 days, was a significant mediator of the pathways from two alcohol interventions to depression symptoms, but not anxiety symptoms.

Conclusions: Improving mental health should be an important target of future interventions for people living with HIV with hazardous alcohol use, and mental health components should be incorporated into alcohol reduction interventions to simultaneously target these co-morbidities among PWH.

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LIST OF ABBREVIATIONS AND ACRONYMS

AIC	Akaike's Information Criterion
AIDS	Acquired Immunodeficiency Syndrome
AR	Autoregression
aRR	Adjusted Risk ratio
ART	Antiretroviral therapy
AUD	Alcohol use disorders
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
BI	Brief Intervention
BIC	Bayesian Information Criterion
CBT	Cognitive Behavioral Therapy
CDT	Cognitive Dissonance Theory
CFI	Comparative Fit Index
CI	Confidence Interval
CIWA	Clinical Institute Withdrawal Assessment of Alcohol
CoI	Combined Intervention
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
FIML	Full information maximum likelihood
FSW	Female sex workers
GAD-7	Generalized Anxiety Disorder-7
GEE	Generalized estimation equations

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Diseases, Tenth Revision
LMIC	Low- and middle-income countries
MAR	Missing at random
MCAR	Missing completely at random
MD	Mean difference
MET	Motivational Enhancement Therapy
MI	Motivational interviewing
MINI	Mini-International neuropsychiatric interview
MNAR	Missing not at random
MSM	men who have sex with men
PEPFAR	President's Emergency Plan for AIDS Relief
PHQ-9	Patient Health Questionnaire-9
PWH	People with HIV/AIDS
PrEP	Pre-exposure prophylaxis
PWID	people who inject drugs
QIC	Quasi-likelihood under the independence model criterion
RCT	Randomized Controlled Trial
REDART	Reducing Hazardous Alcohol Use & HIV Viral Load: A Randomized Controlled Trial (RCT) in ART Clinics in Vietnam
RMSEA	Root Mean Square Error of Approximation
RNA	Ribonucleic acid

RR	Risk ratio
SAVA	Substance abuse, Violence and AIDS epidemics
SD	Standard deviation
SEM	Structural equations modeling
SOC	Standard of care
SPT	Self-perception Theory
TLFB	Timeline FollowBack
TLI	Tucker–Lewis index
UNAIDS	United Nations Programme on HIV/AIDS
UNC	University of North Carolina
US	United States
WHO	World Health Organization

CHAPTER 1. INTRODUCTION AND SPECIFIC AIMS

Mental health disorders are the number one comorbidity among people with HIV (PWH)[1,2]. The most common mental disorders affecting PWH are depression and anxiety disorders, with as many as 47% and 39% of PWH diagnosed with depression and anxiety disorders, respectively[3-5]. Depression and anxiety predict suboptimal adherence to antiretroviral therapy (ART)[6-8], which in turn can lead to viral failure. Indeed, PWH with depression and/or anxiety have significantly worse health outcomes, such as accelerated progression to Acquired Immunodeficiency Syndrome (AIDS) and increased mortality rates[9-13].

The prevalence of hazardous drinking is also very high among PWH, and almost half of PWH are classified as hazardous drinkers[14]. Hazardous drinking is defined the quantity or pattern of alcohol consumption that increases adverse health outcomes for an individual[15], and these thresholds vary from studies to studies. Hazardous alcohol consumption correlates with a lack of viral suppression through reduced adherence and is strongly associated with high morbidity and all-cause mortality[16,17]. Hazardous drinking also significantly increases the risks of depression and anxiety[18-21], and many studies showed that high levels of alcohol use and common mental health disorders such as depression and anxiety frequently coexist among PWH[22-24]. Therefore, it is crucial to study the relationship between alcohol use, depression, anxiety and viral suppression among HIV-infected hazardous drinkers. Although there is evidence of an association between depression, anxiety and viral suppression among PWH[25-27], to my knowledge no studies have looked at this association among PWH who are hazardous drinkers. And since hazardous drinking, depression and anxiety are common comorbidities of PWH, it is also very important to

understand whether depression and anxiety interact with alcohol use to affect HIV outcomes, especially among hazardous drinking PWH.

Motivational Enhancement Therapy and Cognitive Behavioral Therapy are psycho-social intervention approaches that have been widely used to reduce alcohol consumption among PWH[28-30]. Motivational Enhancement Therapy (MET) is a directive, client-centered counseling style that facilitates behavioral change by exploring and resolving ambivalence and elicits clients' own motivation for change[31]. Cognitive Behavioral Therapy (CBT) focuses on modifying maladaptive cognitions, beliefs, behaviors and developing coping skills[32]. It is based on the principles that different learning processes mediate the relationship between environmental stressors and behavioral disturbances. Interventions using MET and CBT are effective in reducing alcohol use among PWH[28-30]. However, little is known about the impact of CBT/MET alcohol reduction interventions on mental health among HIV patients. It is unclear whether reduced alcohol consumption as a result of the interventions can also improve mental health status for hazardous drinking participants. Studying the mechanism through which alcohol reduction interventions affect depression and anxiety over time will help design appropriate interventions that produce the most health benefits for this population.

The proposed study will analyze longitudinal data from the parent study: *Reducing Hazardous Alcohol Use & HIV Viral Load: A Randomized Controlled Trial (RCT) in ART Clinics in Vietnam (REDART) (Grant No. 1R01DA037440-01)*. REDART is a three-arm randomized controlled trial conducted among clients of 7 ART clinics in Thai Nguyen, Vietnam. Four hundred and eleven hazardous drinking PWH in Thai Nguyen were randomly assigned to receive either a combined intervention (CoI) based on MET and CBT approaches (with 6 face-to-face sessions and 3 optional group sessions), a brief intervention (BI) (with 2 face-to-face

sessions and 2 booster phone sessions), or a standard of care (SOC) condition. Participants in the standard of care arm received only referrals to alcohol treatment and infectious diseases treatment. In REDART, hazardous drinkers were defined as female PWH who scored 3 points or more and male PWH who scored 4 points or more on the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) scale[33].

The specific aims of my proposed research are to:

Aim 1: Evaluate the longitudinal association between mental health symptoms (depression and anxiety symptoms) and two HIV outcomes (viral suppression and complete ART adherence) among ART clients with hazardous alcohol use in Vietnam

***Sub-aim 1*:** Determine whether alcohol dependence modifies the longitudinal association between depression, anxiety symptoms and these HIV outcomes

Aim 2: Describe the changes in depression and anxiety symptoms of ART clients who are hazardous drinkers in the parent trial over time, and assess the impact of two evidence-based alcohol-reduction interventions on depression and anxiety symptoms at 3, 6, and 12 months post-intervention, comparing the effects of the two interventions to each other and to the standard of care (SOC) group

Aim 3: Examine the mediating role of alcohol use in the pathway from the two alcohol-reduction interventions to depression and anxiety symptoms of participants at the last follow-up visit

Findings from this study will provide important insight into the impact of alcohol reduction interventions on mental health and the association between depression and anxiety on HIV outcomes over time among PWH with hazardous alcohol use. By identifying the roles that

alcohol use plays in these relationships, we can then design more effective and comprehensive interventions to improve mental health and HIV outcomes for hazardous drinking PWH.

Dissertation structure

In Chapter 1, I present the specific aims and an overview of the proposal. In Chapter 2, I describe the literature on hazardous alcohol consumption, depression and anxiety among PWH globally and in Vietnam. I also discuss literature on the relationship between hazardous drinking, mental disorders and HIV outcomes (ART adherence and viral suppression) among PWH. In Chapter 3, I discuss the theoretical framework underlying my hypotheses as well as my conceptual model. Next, in Chapter 4, I present the methods of the proposed study, including study design, measures and statistical methods to analyze the aims. Chapter 5, 6 and 7 present the detailed background, methods, results and discussion for Aim 1, 2 and 3 in manuscript format, respectively. I end the dissertation with Chapter 8, which provides an overall discussion of study findings and conclusions.

CHAPTER 2. BACKGROUND AND LITERATURE REVIEW

In this chapter, I present the literature related to my proposed research, including existing research on depression, anxiety and alcohol use among PWH and their detrimental effects on patients' health globally and in Vietnam. In the first section, I discuss the global burden of depression and anxiety for PWH and the negative effects on health outcomes of these mental disorders. Next, I present the literature related to alcohol use in this population, describing the intersection of depression, anxiety and alcohol use in determining PWH's health. I also discuss CBT and MET – two alcohol reduction approaches that have been used widely for people with alcohol use disorders. Finally, I introduce the context of the study setting – Vietnam, and present research that have been done in the area of depression, anxiety and alcohol use disorders among Vietnamese PWH.

2.1. Global burden of depression and anxiety among PWH

Depression and anxiety disorders are the most prevalent mental disorders, affecting more than 500 million people of all ages around the world[34].

Depression is a disorder characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration[34]. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), depressive disorders cover a broad spectrum of disorders, such as disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder and substance/medication-induced depressive disorder[35]. For example, a diagnosis of major depressive disorder requires a two-week period of a depressed mood and at least four other

symptoms among the following symptoms: significant weight change or appetite disturbance, sleep disturbance, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, inappropriate guilt, impaired concentration and suicidal ideation or behaviors[35]. The total number of people living with depression globally increased by 18.4% between 2005 and 2015.[36] Currently it is estimated that 4.4% of the world population is suffering from depression[34]. Depression is among the top three largest contributors to all global disabilities by the World Health Organization (WHO), accounting for 7.5% of all years lived with disability[37].

Anxiety disorders are characterized by feelings of excessive fear and anxiety[34]. Common anxiety disorders include Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Panic Disorder, Agoraphobia and Social Phobia[38]. An estimated 260 million people live with anxiety disorders, and this number has increased by 14.9% from 2005 to 2015[34]. In 2016, anxiety disorders were ranked 8th among the leading causes of disability by WHO[34].

Depression and anxiety disorders are also the two most common mental disorders affecting PWH. HIV infection imposes significant psychological burdens on patients, and PWH are significantly more likely to have mental disorders, compared to HIV-negative individuals[39-42]. For example, data from an HIV cohort in Sweden showed that males with HIV had 3 to 4-fold higher odds of being diagnosed with depression or anxiety disorders, while women had 1.6 to 2-fold higher odds of being diagnosed with depression and anxiety disorders, than men and women who were not living with HIV[43]. Indeed, PWH suffer from numerous life challenges and stressors associated with HIV infection, including health-related concerns, financial difficulties as well as discrimination, stigma and lack of social support[44-49]. Moreover, HIV infection has direct effects on the central nervous system, causing structural deficits that are associated with depression and anxiety[50,51]. A review by Del Guerra et al. showed that HIV infection activated

infected immune system cells such as monocytes, microglia and produced toxic viral proteins and infectious virions in the central nervous system[52]. These pathologies in turn interacted with psychological factors to induce depressive states[52].

Up to 67% of PWH have depression symptoms[53-55], and the prevalence of PWH who screened positive for depression ranges from 26.0% to 54.2%, depending on the population, assessment tool and cut-off point for a positive screening result[4,5,56-59]. The prevalence of PWH having any anxiety disorder or having clinically relevant anxiety scores is also high, ranging from 20.3% to 65.8%, depending on the specific types of anxiety outcomes, and whether anxiety was based on a clinical diagnosis or self-reported symptoms[4,5,57,58]. A study in the US among a large nationally representative sample of HIV patients taking ART used the Associated Disabilities Interview Schedule-DSM-IV interview to assess mental health and found that 33.43% of HIV-positive men and 23.74% of HIV-positive women met the criteria for any anxiety disorder, respectively[60]. Depression and anxiety are significant burdens for PWH living in less developed countries. For example, a systematic review using data from 23 studies in Sub-Saharan Africa reported 31.2% and 18.0% as pooled estimates of the prevalence of depressive symptoms and major depression among PWH, respectively[6]. In these studies, major depression was determined through various diagnostic interview tools, such as the Mini-International neuropsychiatric interview (MINI), or the Prime-Mental Disorders mood module.

Despite significant advancements in HIV research including treatment as prevention, pre-exposure prophylaxis (PrEP) and HIV self-testing, depression and anxiety disorders among PWH have been on the rise in the last three decades[3,61]. For instance, the percentage of PWH in the United Kingdom with a depression or anxiety disorders based on ICD-10 more than doubled from 1990 to 2014[3]. This increase could be partly due to the actual increase in the number of

new cases, increased awareness among both patients and clinicians and longer life expectancy for HIV patients[3]. Moreover, PWH have to overcome a multitude of barriers to screening for mental health disorders and receiving quality mental health care, including stigma, incarceration and financial difficulties[62-65]. PWH with depression also experience significantly more difficulties assessing accessing care[66].

2.2. Negative effects of depression and anxiety on health outcomes of PWH

There are multiple ways through which depression and anxiety negatively impact PWH's health. Depression and anxiety among PWH can impair problem-solving skills, reduce economic productivity, damage social relationships, exacerbate social isolation and stigma, and increase the risk for suicidality[67-69]. Depression and anxiety disorders may also increase the prevalence of occupational role dysfunction and self-reported physical disability across multiple cultures[70]. A study among a sample of HIV patients in Uganda showed a 30-fold increase in the odds of suicidality, which included both suicidal ideation and attempted suicide, for those with a depressive disorder diagnosis, while generalized anxiety disorder was found to be a significant correlate of suicidality in the univariate analysis but not in the multivariate analysis[69]. In this study, depression and anxiety disorders were assessed using the MINI questionnaire - a modular DSM-IV-based structured interview. In addition, it has been well-established that depression, anxiety symptoms and disorders are significantly associated with poor ART adherence. Systematic reviews and meta-analyses showed PWH who had depression symptoms had from 42% to 55% lower odds of achieving ART adherence, while anxiety symptoms were associated with a 1.61 times increase in the odds of poor adherence[6,71,72]. Several psychosocial factors have been evaluated as mediators in the pathway between depression and poor adherence, including concentration difficulties, increased concerns about the negative effects of ART, avoidant coping

and thoughts of death[73-76]. Since inadequate exposure to ART can lead to failure to achieve viral suppression, or undetectable viral load[77], PWH with depression and anxiety symptoms usually have faster progression to AIDS and higher mortality rates[12,67,78,79].

However, there were some differences between depression and anxiety symptoms when the association with viral load was examined. A number of studies have evaluated the longitudinal association between depression and viral load, and they all showed a significant positive association between depression and poor viral load outcomes[12,25-27,80-82]. For example, Nance et al. reported a 29% increase in relative viral load among PWH with depression symptoms, when compared to PWH without depression symptoms[81]. Another study in the US found that each 25% increase in the percentage of days with depression during the follow-up period was associated with a 5% increase in the risk of a detectable viral load (≥75 copies/ml)[82].

The association between anxiety and viral load outcomes has not been as well studied and findings across the few studies have varied. In a cross-sectional study among PWH in Russia, Amirkhanian et al. only saw a significant positive association between high anxiety scores (measured with the State Anxiety Inventory scale) and detectable viral load in the univariate logistic regression model[83]. After adjusting for gender, substance use (including alcohol use) and sexual behaviors, the association became non-significant[83]. In another study among perinatally HIV-infected adolescents and young adults, participants were screened for psychiatric disorders with the Diagnostic Interview Schedule for Children tool[84]. This study did not see any association between a positive screening result for anxiety disorder and the risk of having more than 1000 copies/ml[84]. On the contrary, Shacham et al found that higher levels of anxiety were significantly associated with greater likelihood of having a CD4 under 200 cells/mm^3 and unsuppressed viral loads[85]. According to a recent systematic review on anxiety disorders among

PWH by Brandt et al., no studies among the 83 articles included in the review examined the association between anxiety and viral outcomes.

2.3. Alcohol use disorders among PWH

Alcohol use is a leading risk factor for premature mortality and disability worldwide, accounting for 3 million death each year globally[86]. There are various terms used to classify hazardous and heavy alcohol use. Hazardous drinking is defined the quantity or pattern of alcohol consumption that increases adverse health outcomes for an individual[15]. Alcohol Use Disorder Identification Test (AUDIT) is among the most commonly used questionnaires to screen for hazardous drinking, with a cut-off point of 8 indicating hazardous alcohol use[87]. Heavy alcohol use is defined as having than 14 drinks per week for men (or >4 drinks per occasion); more than 7 drinks per week for women (or >3 drinks per occasion)[88]. In the scope of this proposed study, I use hazardous alcohol use as a general term indicating hazardous, heavy and harmful drinking, unless a specific term was used in the studies being cited.

Alcohol use disorder is, on the other hand, a clinical diagnosis, defined as problematic patterns of alcohol use leading to clinically significant impairment or distress, as manifested by at least two among a list of 11 symptoms within a 12-month period[35]. Some examples of these symptoms include taking alcohol in larger amounts or over a longer period than was intended, a persistent desire or unsuccessful efforts to cut down or control alcohol use, or recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school or home. Alcohol dependence - a more severe type of alcohol use disorder – is defined as a strong desire to consume alcohol, difficulties in controlling its use, and persistent use despite harmful consequences[15,89].

Studies using the AUDIT scales showed that between a quarter to almost half of PWH are hazardous drinkers[14,90,91]. The HIV cost and services utilization study in the US found that the prevalence of heavy alcohol use (defined as five or more drinks on ≥ 4 days in the previous 4 weeks) among PWH are twice as high as those of the general population[92]. Similarly, Silverberg et al. found that 48% of HIV patients had at least one binge drinking episode (defined as 4 drinks or more for women and 5 or more for men in a single day), and 23% had more than three such episodes in the last 30 days[14].

Hazardous alcohol use can have multiple potential harmful effects on PWH. First, higher levels of alcohol consumption is linked to increased risky sexual behaviors[93]. Alcohol use can lead to cognitive impairment and reduced perceptions of personal risks[94,95]. Compared with drinkers with neutral expectations about alcohol's effect on sex, drinkers who had favorable attitudes about the effects of alcohol on sex were more likely to report drinking alcohol before sex and were more likely to have casual partners, multiple partners and/or condomless sex after drinking[94-96]. For example, a study in Brazil found that PWH with daily alcohol use had had an 11-fold increase in the odds of inconsistent condom use, compared to PWH who never consumed alcohol[93]. Second, alcohol can negatively affect HIV treatment by reducing adherence and increasing the risk of treatment failure[16,97-100]. A systematic review totaling over 25,000 HIV patients showed that alcohol drinkers were only half as likely to be classified as adherent, compared to with abstainers, and the effects became stronger when the levels of drinking increased[99]. Finally, alcohol can directly compromise the immune system and damage the liver, thereby leading to a worsened course of HIV/AIDS[101,102]. Hazardous drinking is associated with higher viral loads, higher odds of detectable viral load and viral rebound (defined as viral load

above the limit of detection of the laboratory test)[103-106]. Furthermore, worse liver fibrosis has been observed among PWH who are hazardous drinkers, compared to moderate drinkers[101].

2.4. The intersection of depression, anxiety and alcohol use among PWH

Hazardous drinking can lead to increased risk of depression and anxiety, either directly through the cognitive and biochemical changes associated with alcohol intake and withdrawal that lead to depressive and anxiety symptoms, or indirectly through other social consequences of hazardous drinking, such as job loss[18-21,107]. Indeed, PWH who are hazardous and binge drinkers have been shown to be more than 2 times more likely to meet criteria for clinical depression, compared to those who are non-hazardous drinkers[108]. At the same time, depression and anxiety influence drinking behaviors. Increased sensitivity to anxiety and depression can lead to hazardous drinking among PWH through emotional dysregulation, which is defined as difficulties regulating emotions and controlling behaviors[109]. More depressive symptoms in HIV patients are associated with higher levels of alcohol consumption, especially among men[110,111]. In addition, Regier et al. reported that people with any anxiety disorder had a 50% increase in the odds of having an alcohol disorder[24].

Given this strong association, depression, anxiety and hazardous drinking often co-exist among PWH[21-24,105]. Braithwaite et al reported that 10.6% of all HIV patients in their sample had both depression symptoms and harmful alcohol use[22]. In this study, depression symptoms were assessed with the Patient Health Questionnaire (PHQ-9) and harmful alcohol use was defined as having a score of 4 or more on the AUDIT-C questionnaire. Similarly, a study by Fojo et al. found that among PWH who had moderate to severe symptoms of depression, 62.7% had moderate to heavy alcohol use[23]. With 36.9 million PWH globally as of 2017[112], the combined

comorbidity of hazardous drinking and common mental disorders such as depression and anxiety are likely to affect millions of people.

Both hazardous drinking and common mental disorders such as depression and anxiety are independently associated with negative health outcomes for PWH, such as poor adherence, failure to achieve viral suppression and higher mortality rates[12,67,72,79,101,103,113]. However, there is a dearth of research on the associations between depression, anxiety and viral load among PWH who are hazardous drinkers. Since the subgroup of hazardous drinking PWH are even more vulnerable to mental disorders than PWH without drinking issues, it is essential that we understand how common mental health disorders affect viral outcomes among this group.

A few studies have looked at the syndemic effects of comorbidities on HIV viral load and found that viral outcomes were significantly worse when the number of comorbidities increased[114-117]. However, these studies did not examine the specific synergetic impact of alcohol consumption and mental disorders, namely depression and anxiety on viral outcomes. This knowledge gap necessitates research that examines how alcohol use modifies the association between these mental disorders and viral load among hazardous drinking PWH. It underscores the need to design and implement interventions that successfully target both hazardous drinking and mental disorders. This proposed study will also add to the understanding of whether we can address both hazardous drinking and mental health disorders through alcohol reduction interventions.

2.5. CBT and MET interventions to reduce alcohol consumption and their effects on mental health

A number of behavioral interventions have been shown to be effective in reducing alcohol use among PWH with hazardous/heavy alcohol use[28,30,118]. Two commonly used evidence-based approaches are Motivational Enhancement Therapy (MET) and Cognitive

Behavioral Therapy (CBT)[28-30]. MET is based on Motivational Interviewing (MI), but adds to MI by providing personal feedback to clients on their behaviors. MI is a directive, client centered counseling style that facilitates behavioral intervention change by exploring and resolving ambivalence and elicits clients own motivation for change[119]. MI first originated in the context of addiction treatment[119]. MI sessions comprise conversation between the counselor and the patient about change, with the main purpose of strengthening a person's motivation and commitment to change[119]. CBT, on the other hand, consists of a group of psychological therapies that aim to solve negative emotions and dysfunctional behaviors by acknowledging the effects of the environment, cognitions, language and human learning on behaviors[120]. CBT assumes that all humans maintain their behaviors by the same psychological principles, and these behaviors can be changed through social learning and therefore focuses on skill-building[120].

Many promising alcohol reduction interventions drawing on both MET/MI and CBT have reduced alcohol consumption, increased condom use and improved ART adherence[28,30,121]. For example, Chandler et al. tested the effects of a brief intervention, which is based on both MET and CBT among women living with HIV, and reported a significant decrease in the number of drinking day in the treatment group[28]. Another intervention combining MET and CBT among HIV-positive men and women in New York was effective in improving adherence and viral load, although there were no significant effects on alcohol use outcomes[30].

A systematic review of different alcohol reduction interventions in the general population reported overall improvements in mental health and social functioning among participants receiving the interventions being studied[122]. The mental health outcomes evaluated included psychosocial stress levels, anxiety and depression symptoms, self-confidence, contentment with one's life situation, prevalence of psychiatric episodes and duration of in-patient hospital days.

Among these studies, only one evaluated depression and anxiety symptoms as mental outcomes of the intervention[123]. This study examined the effects of a detoxification program on health outcomes of 160 patients with alcohol dependence in the United Kingdom. Alcohol dependence was evaluated in a clinical setting with The Severity of Alcohol Dependence Questionnaire, with scores of 31 or more indicate severe dependence on alcohol. It found that the program produced significant improvements in depression and anxiety symptoms at 6-month follow-up and improvements in anxiety symptoms at 1-year follow-up[123].

Little is known about the specific impacts of MET and CBT on mental health, especially among HIV patients. It is critical to understand if and how alcohol reduction interventions can improve depression and anxiety symptoms of participants. These interventions can either directly influence depression and anxiety through the improvements of coping skills, motivation to change and self-confidence. They can also produce indirect impacts through the reduction of alcohol use. Alcohol interventions that simultaneously improve mental health of participants will be a lot more cost-effective and helpful for PWH who are hazardous drinkers.

2.6. Study context: Vietnam

Vietnam is a country located in South East Asia, with an estimated population of more than 96 million people[124]. In 1975, the North and the South of the country merged to form the Socialist Republic of Vietnam[125]. Since then, Vietnam has gone through rapid socio-economic developments. The big economic reforms (named "Đổi mới") started in 1986, focusing on shifting the country's economy from a centralized economy based on public ownership to a multi-sector economy based on the market[125]. These reforms spurred rapid economic growth in Vietnam and transformed the country into a lower-middle income country in 2010, according to World Bank's ranking[126].

Figure 2.1. Map of Vietnam

(Source: https://www.lonelyplanet.com/maps/asia/vietnam/)

The healthcare system in Vietnam is a mixed public-private provider system that operates at four levels: central level, provincial level, district level and commune level[127]. The Ministry of Health is the governmental agency leading the system at the central level. Along with economic growth, life expectancy at birth in Vietnam has increased 6 years, from 70 to 76 years old between 1990 and 2017[128]. The HIV epidemic in Vietnam started in 1990, when the first HIV infection case was found in Ho Chi Minh city[129]. By 1998, new HIV cases were reported in all provinces and cities of the country. Currently it is estimated that there are about 230,000 PWH in Vietnam[130]. The epidemic is still concentrated among high-risk groups, such as people who inject drugs (PWID) and men who have sex with men (MSM)[129]. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that the prevalence of HIV in the general population in 2018 was 0.3%[130]. According to national data in 2015, 23% of PWID were infected with HIV[129], and the National Integrated Biological and Behavioral Survey in 2009 showed that the prevalence of HIV among MSM in Vietnam ranged from 7.5% to 21.5%, depending on the province and whether the participants reported transactional sex or not[131].

In the past, the majority of HIV funding in Vietnam came from international donors. For example, of the total US$137.5 million spent on HIV programmes in Vietnam in 2015, 36% was from the USA's President's Emergency Plan for AIDS Relief (PEPFAR), while another 14% was from the Global Fund to Fight AIDS, Tuberculosis and Malaria[132]. However, due to the recent transition of the country from a lower income group to the lower-middle income group, a substantial amount of funding for HIV programmes from international funds has been withdrawn [132]. In response to these changes, the Vietnamese government has embraced a growing financial and programmatic responsibility for addressing the HIV continuing epidemic. Towards this end, the government aims to provide 100% health insurance coverage for PWH by 2020[133]. In line with the 90-90-90 targets launched by UNAIDS, which aimed to have 90% of PWH know their status, 90% of PWH knowing their status being on treatment and 90% of people on treatment being virally suppressed (or having undetectable viral load), in 2017 Vietnam started implementing the "treat all" policy, regardless of patients' CD4 level[134]. However, PWH in Vietnam still face significant barriers to care due to health inequalities, discrimination, stigma and other mental comorbidities[135-138].

2.6.1. Alcohol use in Vietnam

Alcohol use and alcohol-related problems are common in Vietnam, especially among men[139]. Alcohol home brewing is a popular practice here, with some private homes producing hundreds of millions of liters annually[140,141]. According to WHO, it is estimated that 4.7% of the population in Vietnam (8.9% of men, 0.9% of women) have an AUD, and 2.9% of the population (5.9% of men and 0.1% of women) are alcohol dependent[142]. These estimates are slightly higher than the prevalence of AUD and alcohol dependence in the WHO Western Pacific Region where Vietnam is located, which are 4.6% and 2.3%, respectively[142]. In a nationally

representative sample survey of more than 14,000 Vietnamese, about 40% of men and 2.1%-3.8% of women were classified as hazardous drinkers, respectively[141]. In Vietnamese drinking culture, alcohol intoxication is expected and normalized during social gatherings, where drinkers press each other to drink to intoxication[140]. As a consequence, alcohol use is a leading risk factor for death and disability in Vietnam[142]. Indeed, Vietnam's score in alcohol-attributable years of life lost is ranked at level 5 – the highest level according to WHO ranking[142]. Alcohol is estimated to be responsible for 71.7% and 37.7% of liver cirrhosis cases among men and women in Vietnam, respectively[142].

Hazardous alcohol use is even more prevalent among PWH in Vietnam. A study by Tran et al. in 2013 reported a prevalence of hazardous drinking of 30% and a prevalence of binge drinking of 22% among PWH on ART in Vietnam[137]. Patients face multiple cultural and contextual barriers at different levels to reducing alcohol use[143,144]. For example, the widespread availability and affordability of alcohol makes it very easy for them to purchase and consume alcohol[143,144]. Moreover, high social pressure to drink and the connection of drinking with social support create additional challenges for PWH to reduce alcohol consumption[143].

2.6.2. Mental health and alcohol use among PWH in Vietnam

Depression and anxiety symptoms affect a large proportion of PWH in Vietnam[145,146]. Key populations, including PWID and MSM are highly stigmatized in Vietnam[135,138,147], and experiences of stigma and discrimination are closely linked to anxiety and depression symptoms[138]. A study among 400 HIV patients in Ho Chi Minh city, Vietnam showed that the prevalence of depression and anxiety symptoms was 36.5% and 10.5%, respectively[145]. Another study among HIV-positive PWID in Vietnam found that 44% of participants had severe depressive symptoms, while 25% had mild to moderate symptoms[146]. Depression has been linked

to challenges in accessing healthcare services, poor health-related quality of life and increased mortality among PWH in Vietnam[66,148,149]. However, the literature on anxiety disorders among PWH in Vietnam is scarce. In addition, no research has looked at the longitudinal association between depression, anxiety and viral load among PWH in general and hazardous drinking PWH in particular.

Some studies have examined the association between alcohol use and common mental disorders among PWH in Vietnam, but found inconsistent results. Thai et al. found no significant association between symptoms of mental disorders and alcohol use among PWH in Vietnam[145]. Depression and anxiety symptoms were measured using the Center for Epidemiologic Studies–Depression scale and Phan Vietnamese Psychiatric Scale-Anxiety subscale, respectively, while alcohol use was assessed with the AUDIT scale. However, another paper published by Levintow et al. among PWH in Thai Nguyen reported a protective effect of drinking against depressive symptoms[146]. The paper suggested that these findings may be because the absence of alcohol use in a context where alcohol is highly normative, is a potential indicator of social separation, isolation and the lack of social support from friends and family and therefore depression[146].

Given the lack of research on depression and anxiety among PWH who are hazardous drinkers, studies that evaluate the association between these common mental disorders and viral load, the potential impact of alcohol reduction interventions on mental health as well the roles that alcohol use play in these relationships are critically needed. Understanding how the comorbidities of HIV infection, alcohol use and mental disorders interact to affect PWH's health will help maximize the benefits for PWH who have both hazardous drinking and mental disorders, not only in Vietnam but also around the world.

CHAPTER 3. THEORETICAL BACKGROUND AND CONCEPTUAL MODEL

In this chapter, I present the theoretical background of my proposed research and the conceptual model that frames my hypotheses. In the first section, I present the Transactional Model of Stress and Coping, and discuss how it relates to the association between mental disorders and viral outcomes. Next, in section 3.2, I introduce the Syndemics Theory and explain how it informs one of my research questions. In section 3.3, I provide a theoretical background of CBT and MET, and discuss how these approaches can affect mental health outcomes. Finally, I present the conceptual model integrating all the theories mentioned above.

3.1. The Transactional Model of Stress and Coping

Research has established a robust association and a bidirectional relationship between depression, anxiety and stress[150,151]. Stress is an important cause of depression and anxiety, while depression and anxiety can make one more vulnerable to stress[150-152]. PWH usually suffer from stress from numerous sources Individual-level stressors include HIV infection, other health-related concerns, injection drug use, low socioeconomic status, while discrimination, stigma and the lack of social support are among the most common environmental level stressors[44-48].

The Transactional Model of Stress and Coping is a framework that suggests the pathways from stressors to coping to mental well-being, functional status and health behaviors[153]. According to the framework, developed by Lazarus and Cohen, the experience of stress can have a negative impact on physical health and functional status through direct physiological impacts on health or through indirect effects via maladaptive behaviors, such as alcohol drinking or non-

adherence to treatment[153]. On the first hand, empirical studies have shown that stressors and negative emotions can lead to physiological changes[154,155]. Chronic stress and depression promote immune dysfunction and worsen the body's responses to infectious diseases by increasing peripheral production of proinflammatory cytokines[155]. Studies have reported an association between chronic stress and poorer responses to vaccination, suppression of lymphocyte production as well as increased susceptibility to infection[156,157]. Among PWH, psychiatric illnesses can alter the amount and level of activation of lymphocytes, which play a crucial role in the regulation of HIV infection[158]. For example, depression and anxiety are associated with more rapid decline in CD4 lymphocyte counts, higher activated CD8 lymphocyte counts, lower natural killer cell activity and higher viral loads among PWH[57,158-160]. On the other hand, stress can lead to maladaptive behaviors such as hazardous alcohol use and non-adherence, which are also closely linked with poorer physical and mental health. For example, hazardous alcohol use is significantly associated with increased risk of depression, anxiety, lower CD4 counts and higher viral loads[20,21,103,106].

Interventions applying the Transactional Model of Stress and Coping have successfully decreased stress hormones, reduced depression, increased production of T-cells and decreased HIV viral load[161-163]. Based on this theory, I hypothesize that there is a relationship between depression, anxiety symptoms and ART adherence and viral suppression, such that hazardous drinking PWH with symptoms of depression and anxiety are more likely to poor adherence and less likely to achieve viral suppression. However, due to the differences in characteristics of anxiety and depression symptoms, and the weak evidence of the association between anxiety and viral outcomes published in the literature[83,84], I expect differential effects. Specifically, I

anticipate that compared to anxiety symptoms, depression symptoms will have a stronger association with HIV outcomes (ART adherence and viral suppression),

3.2. The Syndemics Theory

The syndemic approach to a public health problem explains why certain diseases and conditions usually co-occur, and to identify the pathways through which they interact to enhance the negative effects of diseases[164]. This approach in public health was first discussed by Singer in the context of the Substance abuse, Violence and AIDS (also known as SAVA) epidemics, which posed critical threats to the lives of PWH in the US[165]. According to Singer, there are certain social, political and environmental factors that facilitate the clustering of two or more diseases[164]. However, a syndemic is different than the mere co-existence of two or more diseases in the same patient. The term "syndemic" is defined as a dynamic relationship involving two or more epidemic diseases or other disorders and the socioenvironmental context that promotes their interaction[166]. Singer listed three criteria of a syndemic: (1) the clustering of two or more diseases in a population; (2) the contextual and social factors leading to this clustering and (3) the adverse effects on health and increased burden of the affected populations due to the interaction of the social and health conditions[164]. The Syndemics Theory posits that the co-existence and synergistic interaction of more than one adverse condition in a patient produce worse health outcomes than if each of the conditions exists separately[164,166]. There are a number of mechanisms through which comorbidities tend to cluster and interact to worsen health outcomes. Syndemic interactions include alterations of the physical body, alterations of the emotions, reassortment of genes and interactions of medical treatment[164]. First, the co-existence of two different pathogens can exacerbate the virulence of each other and increase susceptibility of the host to other infectious agents. In the case of HIV/AIDS, HIV infection significantly

increases the incidence of genital ulcer disease and gonorrhea due to high levels of immunosuppression among HIV patients[167]. The combined effects of socioenvironmental and biological factors can also enhance the contagiousness of diseases and lead to higher health burden in the population. For example, MSM and PWID living with HIV usually suffer from stigma and discrimination from the society, which in turn are closely associated with depression, anxiety and alcohol use disorders[45-47,168-170]. Indeed, a number of studies have looked at comorbidities in the context of HIV infection from the syndemic perspective, since PWH usually suffer from multiple comorbidities such as opportunistic infections due to weakened immune systems, substance abuse, violence and mental disorders[114,116,117,171-174]. One of the aims of this proposed research is to look at the potential synergetic impact of depression, anxiety symptoms and alcohol dependence on HIV outcomes of ART clients. The Syndemics Theory informs the hypothesis that alcohol dependence interacts with depression, anxiety symptoms to worsen ART adherence viral load outcomes, possibly through both biological and biosocial mechanisms.

3.3. Theoretical foundations of Cognitive Behavioral Therapy and Motivational Enhancement Therapy

CBT originated from the first behavioral models developed by Ellis and Beck in the 1960s and 1970s[175,176]. Ellis' rational emotive behavior therapy, which challenged patients' thoughts and guided them towards more rational thinking was the first type of cognitive-based psychotherapy[176]. In 1976, Beck developed cognitive therapy, which emphasized the central role of cognitive processes in treating emotional disorders[175]. Cognitive Theory is the theoretical background underlying CBT. According to Cognitive Theory, psychological disturbances are considered maladaptive schematic representations of oneself and the world around him or her[177]. These psychological states stem from biases in the information-processing system that lead to maladaptive thoughts, behaviors and physiological responses[177]. In order to help patients recover

from psychopathological states, the correction of these biased cognitive process specific to the disorders being treated is required. A critical component of cognitive therapy is therefore training patients to identify and modify their cognitive errors. More recently, CBT has been widely applied to alcohol and other substance use disorders[178], and has been effective across a diverse sample of participants and disorders. A meta-analysis examining 53 randomized controlled CBT trials for people who had alcohol or drug use disorders reported a significant pooled effect of treatment on alcohol and drug use, with strongest effects of CBT among marijuana users[179].

MET was first developed in 1989 to be used in a multisite clinical trial in the US designed to test a priori client treatment matching hypotheses[180]. MET was based on MI - a client-centered counseling style aiming to change behaviors[181] by strengthening a person's own motivation, readiness and commitment to change[119]. MI was first developed during William Miller's work focusing on behavioral therapies for patients with problem drinking[182]. There are four processes involved with MI: engaging, focusing, evoking and planning[119]. Engaging starts when a client and his provider connect and form a working relationship. The second process, focusing, takes place when both parties decide on the direction of their conversation about change. Evoking, which is the main component of motivational interview, brings out clients' readiness to change through various techniques. Finally, planning is a phase during which the commitment to change and specific plan of action is developed for clients. Cognitive dissonance theory (CDT) and Self-perception theory (SPT) have been proposed as the underpinnings of motivational interviewing[183]. According to CDT, which was originally formulated by Festinger in 1957, the presence of dissonance, or the inconsistency among different cognitions, could lead to a state of tension or discomfort and motivate individuals to change their cognitions to make them consistent[184]. Therapists have used MI to arouse a dissonant state in clients and channeled

their motivation to minimize that state into behavioral changes[185]. The principles and techniques of MI are also grounded in self-perception theory, which was developed by Bem in 1967 as an alternative to CDT. SPT proposes that people who are ambivalent about an issue determine what they believe by listening to themselves[186,187]. Therefore, clients in MI therapy begin to convince themselves of the need to change after attending to their own verbal behavior regarding behavior changes[188]. Recently, Miller proposed a new theoretical framework for MI that consists of a relational and a technical component[183]. The relational component hypothesizes that the relationship between client-counselor and the therapeutic skill of empathetic understanding are critical to the positive behavioral changes in clients. The technical component, emphasizes the role of techniques and proficiencies in delivering MI to clients. This new theoretical framework proposes a direct effect of these two components on behavioral change outcomes as well as the mediating role of change talk, which is clients' motivation and commitment to change[183]. Apart from problem drinking, MI has had positive outcomes among clients with depression and anxiety[189-191]. For example, a qualitative study looking at clients' experiences of MI for generalized anxiety disorder reported an increase in motivation for treatment and change among clients[191]. Another cluster randomized trial found that MI significantly improved depressive symptoms among patients with newly diagnosed major depressive disorder[190].

The parent study used CBT and MET to reduce alcohol use; however, the theoretical backgrounds of these approaches suggest that the readiness to change and coping skills can potentially be helpful in dealing with depression and anxiety.

3.4. Conceptual model, aims and hypotheses

A conceptual model drawing from all the theories and literature background discussed earlier is presented in Figure 3.1. It incorporates the relationships between stressors of PWH,

alcohol use, mental, physical health and CBT/MET interventions. Individual and interpersonal factors such as HIV infection, low socioeconomic status, injection drug use, stigma and lack of social support make PWH more susceptible to alcohol use, depression and anxiety. Alcohol use, depression and anxiety symptoms in turn affect the likelihood of ART adherence and viral suppression. Alcohol use, depression and anxiety symptoms are also closely linked and can interact to exacerbate negative outcomes for PWH. CBT and MET interventions in this study focused on alcohol use among PWH through changing coping skills and readiness to change. They can potentially produce positive impacts on depression and anxiety symptoms either directly or indirectly through reducing alcohol use.

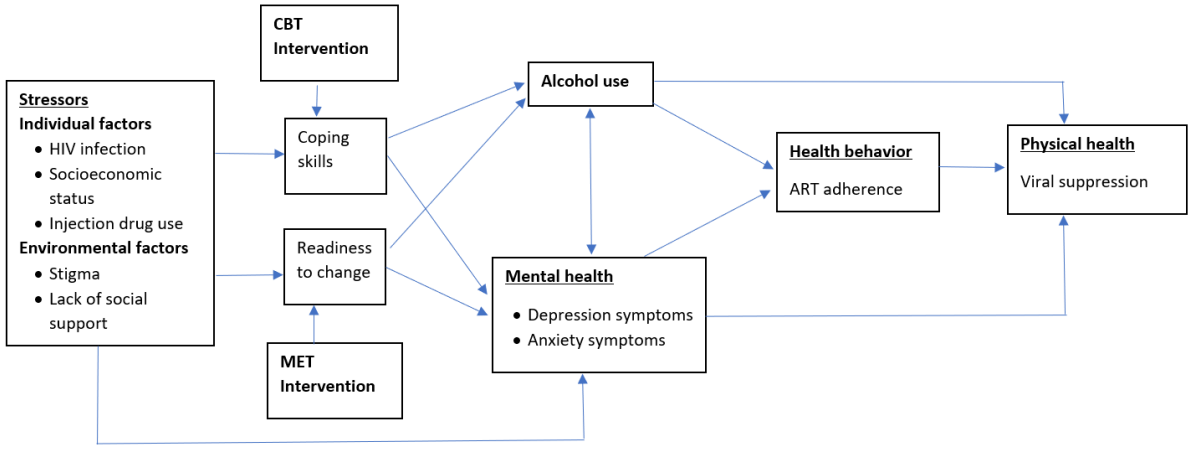


Figure 3.1. Conceptual model

This proposed study has three aims, with each aim answering unique research questions and testing different hypotheses. Depression and anxiety symptoms are two separate constructs in the analyses. Aim 1 is to evaluate the longitudinal association between mental health symptoms (depression and anxiety symptoms) and two HIV outcomes (viral suppression and complete ART adherence) among ART clients with hazardous alcohol use. Sub-aim 1 is to determine whether alcohol dependence modifies the longitudinal association between depression, anxiety symptoms and these HIV outcomes. Aim 2 is to describe the changes in depression and

anxiety symptoms of ART clients who are hazardous drinkers in the parent trial over time, and assess the impact of two evidence-based alcohol-reduction interventions on depression and anxiety symptoms, comparing the effects of the two interventions to each other and to the SOC group. Aim 3 is to examine the mediating role of alcohol use in the pathway from the two alcohol-reduction interventions to depression and anxiety symptoms of participants. The mapping of three aims and underlying theories are shown in Figure 3.2.

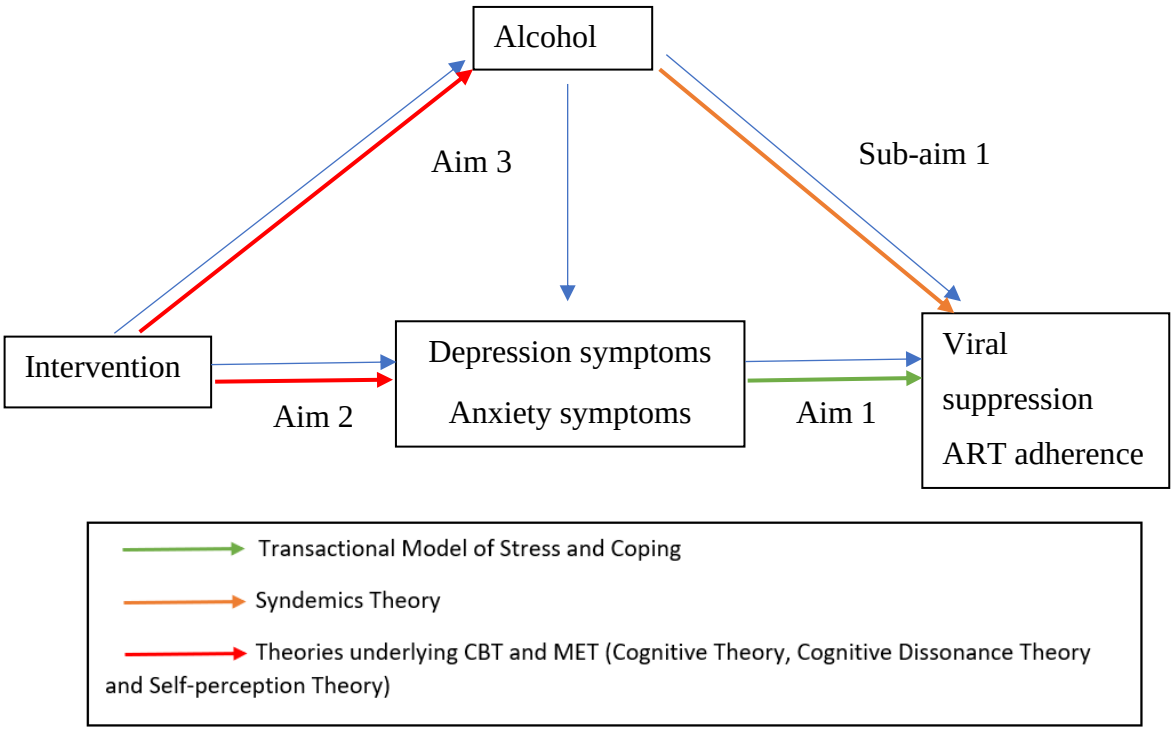


Figure 3.2. Mapping of proposed aims and underlying theories

3.4.1. Aim 1 and Sub-aim 1

Aim 1 of this study is to evaluate the longitudinal association between depression, anxiety symptoms and two HIV outcomes (viral suppression and complete ART adherence), controlling for intervention exposure among ART clients who are hazardous drinkers. Transactional Model of Stress and Coping explains the close link between mental health and physical health outcomes. Therefore, I hypothesize that more severe depression and anxiety

symptoms at one time point will be associated with lower likelihood of viral suppression and ART adherence at the subsequent time point, after controlling for intervention exposure.

Sub-aim 1 evaluates whether alcohol dependence modifies the longitudinal association between depression, anxiety symptoms and these HIV outcomes. Guided by the Syndemics Theory, I hypothesize that the association between depression, anxiety symptoms and viral suppression and ART adherence will be stronger among ART clients with alcohol dependence, compared to those without.

3.4.2. Aim 2

Aim 2 describes the changes in depression and anxiety symptoms of ART clients who are hazardous drinkers in the parent trial over time, and assesses the impact of two evidence-based alcohol-reduction interventions on depression and anxiety symptoms at 3, 6, and 12 months post-intervention, comparing the effects of the two interventions to each other and to the standard of care (SOC) group. I hypothesize that ART clients randomized to both the CoI and BI groups will have significantly fewer depressive and anxiety symptoms at all follow-up time points, compared to those in the control group. Since the contents of BI are also drawn from CBT and MET, I expect that there will be no significant differences in effects on depressive and anxiety symptoms between two groups.

3.4.3. Aim 3

Aim 3 evaluates whether alcohol use is a mediator in the pathway from the interventions to depression and anxiety symptoms. Based on Cognitive Theory, CDT and SPT, CoI and BI are expected to reduce alcohol use among participants in the parent study. Given the association between alcohol use and depression and anxiety[18-21], I hypothesize that participants randomized to either the CoI or BI will over time have significantly lower levels alcohol use at follow-up

time points, compared to the control group; and lower levels of alcohol use in turn are associated with fewer in depressive and anxiety symptoms among participants at subsequent time points. I expect that alcohol use will be a mediator in both the pathway from the interventions to depression symptoms and from the interventions to anxiety symptoms, given the equally strong evidence of the association between alcohol use and both depression and anxiety[18-21].

The analyses in Aim 3 also enable me to determine if there is a significant direct effect of the interventions on depression and anxiety symptoms, after controlling for the effects through alcohol reduction. CBT helps clients identify negative, biased thoughts, modify these cognitive errors and develop alternative coping skills. MET supports self-efficacy and optimism for clients, strengthening their own motivation while expressing empathy for clients' problems. The skills and cognitive changes acquired through CBT and MET framed for alcohol reduction could also be applied to addressing depression and anxiety. Therefore, I hypothesize that alcohol reduction interventions using CBT and MET also have a direct effect on depression and anxiety symptoms at 12 months, after controlling for alcohol use change.

In conclusion, the Transactional Model of Stress and Coping and the Syndemics Theory inform Aim 1 and Sub-aim 1, while the theoretical underpinnings of CBT and MET inform Aim 2 and Aim 3 of my proposed research.

CHAPTER 4. METHODS

4.1. The parent study

This proposed research is a secondary data analysis of the parent study – a NIDA R01, *Reducing Hazardous Alcohol Use & HIV Viral Load: A Randomized Controlled Trial (RCT) in Antiretroviral Treatment (ART) Clinics in Vietnam [REDART]* (PI: Vivian Go PhD: 1R01DA037440-01). This study is a three-arm RCT among hazardous and heavy drinking HIV-infected ART clinic patients in Thai Nguyen, Vietnam. The main goal of the study is to understand the relative effectiveness of two interventions in improving both alcohol- and HIV-related outcomes in resource-limited settings. The three arms are a CoI group, a BI group and a standard of care group. Participants randomized to the standard of care arm received only referrals to alcohol treatment and infectious diseases treatment, as recommended by the Ministry of Health in Vietnam.

The two interventions, which draw from CBT and MET, are compared against each other and compared with the standard of care arm.

4.1.1. Intervention setting

The parent study was implemented in Thai Nguyen, a mountainous, multi-ethnic province located in Northeast Vietnam. The map of Thai Nguyen is shown in Figure 4.1. Thai Nguyen is ranked as the third largest province in the North of Vietnam. It has a population of 1,255,100 people as of 2017, two thirds of whom live in rural areas. The HIV epidemic in Thai Nguyen is primarily driven by injection drug use, with an HIV prevalence among PWID of 31.2%[136]. In 2016, there were 3362 HIV-infected adults and 125 children in HIV care in Thai Nguyen[192].

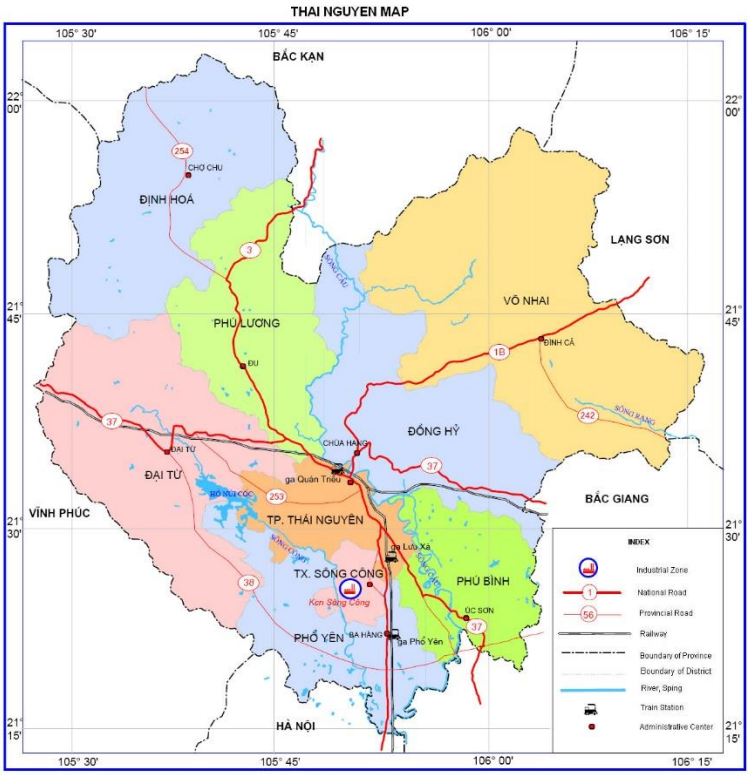


Figure 4.1. Map of Thai Nguyen province

(Source: investinvietnam.vn)

4.1.2. Study design

The purpose of REDART was to compare the effects of the Brief Intervention to a Combined Intervention both against each other and compared with a standard of care arm. Four hundred and forty-one HIV clinic patients with hazardous drinking in Thai Nguyen Province ART clinics were randomized to receive BI (2 face-to-face sessions and 2 booster phone sessions total), CoI (6 face-to-face sessions and 3 optional group sessions), or a standard of care arm. All participants were recruited from 7 outpatient ART clinics in Thai Nguyen with the highest numbers of ART clients, including 6 community clinics and 1 hospital clinic. Each participant had 3, 6 and 12-month follow-up assessments. Data collection was completed in June 2018. Figure 4.2 shows the design of the parent study.

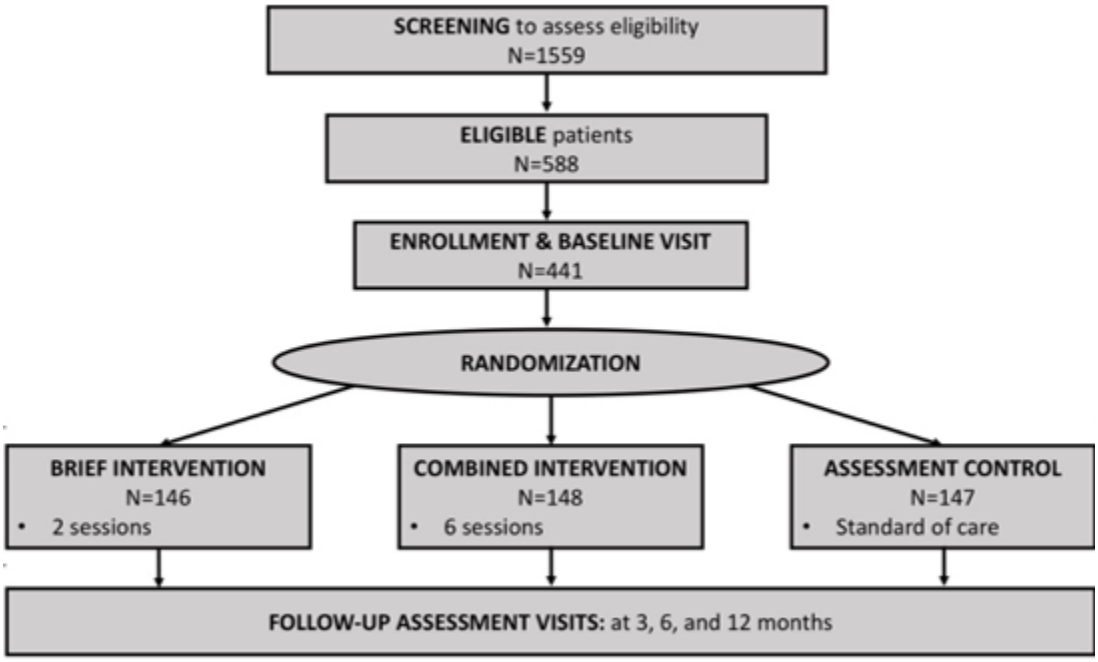


Figure 4.2. Study design of REDART

4.1.3. Description of the interventions and study arms

4.1.3.1. The Combined Intervention

CoI comprised a total of 6 individual face-to-face sessions and 3 optional group sessions for each participant assigned to this arm, with individual sessions occurring approximately 1 week apart. The CoI combined aspects from both MET and CBT. It used a client-centered, motivational interviewing approach and focused on developing positive thoughts and skill-building for alcohol use behavior change, including drinking refusal skills, skills to cope with and manage cravings and triggers. Counselors also reviewed drinking patterns and harmful effects of drinking with patients.

The rationale for combining MET and CBT intervention programs into one overall intervention was based on the study team's formative research results, which indicated that using MET and CBT separately, as they are used in the US, would not be culturally appropriate in the Vietnamese context. Therefore, investigators culturally adapted components of MET and CBT

into this combined intervention to be more applicable to alcohol use behaviors in the Vietnamese context.

There was a 12-week window after each participant's randomization into the study for the participant to complete their intervention sessions. Additionally, there were three optional group sessions that participants assigned to the combined intervention arm could choose to attend any time after they enrolled into the study. The group sessions were informal and could take place anytime within the duration of the study.

4.1.3.2. The Brief Intervention

BI combined elements from both CBT and MET, but condensed them into a 1- or 2-session format[193]. This intervention comprised 2 individual face-to-face sessions and 2 individual booster phone sessions for each participant assigned to this arm. The face-to-face sessions occurred approximately 1 month apart, and a phone session occurred 2-3 weeks after each face-to-face session. Contents of BI sessions also included review of drinking patterns, harmful effects of drinking, and alcohol use behavior change strategies. There was a 12-week window after randomization into the study for the participant to complete their intervention sessions. The cultural adaption of the interventions has been described in detail previously[193].

4.1.3.3. Standard of care arm

Participants randomized to the standard of care arm received only referrals to alcohol treatment and infectious diseases treatment.

A summary of the study arms is shown in Table 4.1.

Table 4.1. Summary of standard of care and intervention arms

	Standard of care	Combined Intervention	Brief Intervention
Standard of Care Services			
Harm reduction services	X	X	X
ART at any CD4 count	X	X	X
Referrals for substance use	X	X	X
Referrals for diagnosis and treatment of Hepatitis B, C, sexually transmitted infections and Tuberculosis	X	X	X
Face-to-face counseling sessions		6 sessions	2 sessions
Phone sessions			2 sessions
Group sessions (optional, up to 3)		X	

4.1.3.4. Training of counselors

Core research staff and study investigators identified potential counselors in Thai Nguyen and provided them with training on HIV, addiction, alcohol use and counseling skills. Potential counselors were assigned to one of the two interventions (BI vs. CoI) and received additional intensive training specific to the assigned intervention.

4.1.4. Participant recruitment and inclusion criteria

Participants were recruited from 7 outpatient clinics in Thai Nguyen. Recruitment was completed in one clinic before moving to the next clinic. Patients who were 18 years and older at each clinic were given information about the project by study or clinic staff and those interested were invited for baseline written informed consent and screening at the baseline visit to determine eligibility. The WHO AUDIT-C survey was included in the screening survey to assess each participant's eligibility for the RCT. Clients with an AUDIT-C score ≥ 4 for men and ≥ 3 for women were considered to have hazardous alcohol use.

Inclusion criteria for participation in the RCT were:

1) a current client on ART at the clinic;

2) an AUDIT-C score ≥ 4 for men; AUDIT-C score ≥ 3 for women (hazardous alcohol use);

3) 18 years of age or older;

4) plan to reside in Thai Nguyen for the next 24 months.

Exclusion criteria for participants were:

1) inability to provide informed consent due to cognitive impairment or having threatening behavior (study staff assessed sobriety);

2) unwilling to provide locator information;

3) unwilling to provide informed consent;

4) currently participating in other HIV, drug use or alcohol program, study, or intervention

Study interviewers introduced the project to each client and, among all those who were interested and were 18 years of age or older, interviewers administered the baseline written informed consent to participate in the baseline questionnaire and conducted the baseline survey among those who consent. The baseline survey was administered to all individuals screened, regardless of eligibility.

For eligible participants only, an enrollment eligibility checklist was used to confirm eligibility. Enrollment written informed consent was also conducted with eligible participants, during which interviewers described the RCT study objectives, procedures, risks and benefits to the eligible participants, and answered any questions. Locator information from the enrolled participant and baseline laboratory specimens from the enrolled participant were collected. Apart

from the baseline survey, enrolled participants also completed the MINI and Timeline FollowBack questionnaire (TLFB), to assess detailed alcohol use in the previous 30 days.

A randomization schedule was generated prior to the first enrollment, using permuted-block randomization with block size of 3, with study arms randomized at a 1:1:1 ratio.

In the end, 441 participants were enrolled in the RCT. 146 participants were randomly assigned to the BI arm, 148 randomly assigned to the CoI arm and 147 randomly assigned to the SOC arm.

4.1.5. Data collection

4.1.5.1. Quantitative assessments

Quantitative assessments occurred at baseline, 3, 6, and 12 months for all participants enrolled in the RCT. All patient questionnaires were administered through face-to-face interviews in a private room at the project facility with trained interviewers. Trained interviewers who were not ART clinic staff administered the questionnaires using computer assisted personal interviewing via tablets. The TLFB alcohol data, however, was recorded on paper then entered manually into a database.

4.1.5.2. Laboratory assessments

Blood samples were collected at baseline, 3, 6 and 12 months for all participants by a trained phlebotomist. At baseline, blood specimens tested for HIV viral load, CD4 level, Hepatitis B (HBV), and Hepatitis C (HCV). At follow-up, HIV viral load was assessed at all visits, and CD4 level was assessed at 12 months only (using the same procedures as at baseline).

4.1.5.3. Allowable visit windows and missed visits

The visit window for a follow-up visit date was defined around the target day on which a visit should ideally occur. The allowable visit window is an extension of the target window and

is the timeframe within which each visit must take place. Late visits within 61-63 days (depending on the follow-up time) of the target day, and early visits within 2 weeks of the target day for the 3 months follow-up and within 4 weeks of target day for the 6 and 12 month follow-up were allowed. Visits that occur outside the allowable visit window are considered "missed."

4.1.6. Ethics

The study was reviewed and approved by the UNC IRB and the local IRB at the Thai Nguyen Center for Preventive Medicine.

All participants received an identification number and only the consent form, tracker form, and tracker computer linked the participant's name to the identification number. Identifiable information of participants was removed from the datasets used for this secondary analysis. Therefore, the risk of confidentiality breach is expected to be negligible in this proposed research.

4.2. Dissertation research

4.2.1. Aims and hypotheses

The aims of this proposed research and hypotheses are presented below:

Aim 1: Evaluate the longitudinal association between mental health symptoms (depression and anxiety symptoms) and two HIV outcomes (viral suppression and complete ART adherence) among ART clients with hazardous alcohol use in Vietnam

- Hypothesis 1: Having more depression or anxiety symptoms is associated with a lower probability of viral suppression and complete ART adherence among hazardous drinking ART clients.

Sub-aim 1: Determine whether alcohol dependence modifies the longitudinal association between depression, anxiety symptoms and these HIV outcomes

- Hypothesis 2: The associations between depression, anxiety symptoms and lower probability of viral suppression are stronger among participants with alcohol dependence, compared to those without.

Aim 2: Describe the changes in depression and anxiety symptoms of ART clients who are hazardous drinkers in the parent trial over time, and assess the impact of two evidence-based alcohol-reduction interventions on depression and anxiety symptoms at 3, 6, and 12 months post-intervention, comparing the effects of the two interventions to each other and to the standard of care (SOC) group

- Hypothesis 3: Hazardous drinking ART clients randomized to the BI and CoI arms will have fewer depression and anxiety symptoms at follow-up time points, compared to participants randomized to the SOC arm.
- Hypothesis 4: There are no significant differences in depression and anxiety symptoms among participants randomized to the BI arm and participants randomized to the CoI arm.

Aim 3: Examine the mediating role of alcohol use in the pathway from the two alcohol-reduction interventions to depression and anxiety symptoms of participants at the last follow-up visit

- Hypothesis 5: Hazardous drinking ART clients randomized to the BI and CoI arms have lower levels of alcohol use at the follow-up visits, compared to participants randomized to the SOC arm. Participants with lower levels of alcohol use at these time points, in turn have fewer depression and anxiety symptoms at 12 months.

4.2.2. Measures

4.2.3.1. Depression and anxiety symptoms

Depression and anxiety symptoms were measured for all participants enrolled in the RCT at baseline, 3, 6 and 12-month follow-up visits.

Depression symptoms were assessed with the Patient Health Questionnaire-9 (PHQ-9) and anxiety symptoms were assessed with the Generalized Anxiety Disorder-7 (GAD-7) scale. The PHQ-9 is a well validated scale used widely to evaluate depression and depression symptoms among various populations in Vietnam, including PWH[149,194-196]. The GAD-7 has also been validated among PWH, and has been used in Vietnamese populations to measure anxiety[197-200]. The PHQ-9 consists of 9 items and the GAD-7 consists of 7 items. Each item is rated on the frequency of the symptoms in the last 2 weeks, with the following answer choices: "Not at all" (0 days), "Several days" (1-7 days), "More than half of the days" (8-10 days) and "Nearly every day" (11-14 days). These options correspond to a score of 0, 1, 2 and 3, respectively. The PHQ-9 score ranges from 0 to 27 (with higher scores indicating higher levels of depression), and the GAD-7 score ranged from 0 to 21 (with higher scores indicating higher levels of anxiety). Participants scoring 4 points or less on the PHQ-9 are considered not to have depression symptoms. A score of 5-9, 10-14, 15-19, and 20 or more in the PHQ-9 indicates mild, moderate, moderately severe and severe depression symptoms, respectively[201,202]. Similarly, for the GAD-7, ranges of 5-9, 10-14 and 15-21 are interpreted as mild, moderate and severe anxiety symptoms[203]. Since classifying continuous data into binary data can result in a loss of power and binary data are less sensitive to change[204], the original continuous scores of depression and anxiety symptoms were used in this dissertation research.

4.2.3.2. Alcohol use

Alcohol use was measured with the MINI and TLFB questionnaire at baseline, 3, 6 and 12 month follow-up visits.

The MINI is a structured diagnostic psychiatric interview for DSM-IV and International Classification of Diseases, 10th revision (ICD-10) disorders developed by Sheehan et al[205]. This questionnaire has 12 alcohol use-related questions and answering Yes to 3 or more indicates alcohol dependence.

The TLFB questionnaire has also demonstrated high levels of validity and reliability to measure alcohol consumption across different cultures[206,207]. Daily alcohol consumption is recorded as number of standard drinks. Percentage of abstinent days (out of the last 30 days) is calculated at each visit. Alcohol dependence determined with the MINI scale will be used as the moderator in Sub-aim 1, while percentage of abstinent days (the primary outcome of the alcohol use in the parent study) will be used as the mediator in Aim 3.

4.2.3.3. HIV viral load and ART adherence

HIV-1 ribonucleic acid (RNA) levels were performed on whole blood samples collected at baseline, 3, 6, and 12 months by using the in vitro nucleic acid amplification test (COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test), by Roche Molecular Systems, for the quantitation of Human Immunodeficiency Virus Type 1 (HIV-1) RNA in human plasma. Viral suppression is defined as having less than 20 copies/ml. Complete ART adherence (self-reported) is defined as no missed pills in the past 3 months. Both HIV viral load and self-reported adherence were measured at baseline, 3, 6 and 12-month follow-ups.

Table 4.2. Summary of key measures

Measure	Role in Aim 1	Role in Aim 2 and Aim 3	Measurement tool	Type	Time of assessment
Depression symptoms	Predictor	Outcome	PHQ-9	Count	All time points*
Anxiety symptoms	Predictor	Outcome	GAD-7	Count	All time points
Intervention exposure	Confounder	Predictor	Assigned at baseline	Categorical	All time points
Alcohol use	Moderator/ Potential confounder	Mediator	MINI TLFB	Binary Continuous	All time points All time points All time points
Complete ART adherence	Outcome	N/A[ɣ]	Questionnaire	Binary	All time points
Viral suppression	Outcome	N/A[ɣ]	Copies of HIV-RNA/ml in blood sample	Binary	All time points
Age	Potential confounder	Potential confounder	Questionnaire	Continuous	Baseline only
Marital status	Potential confounder	Potential confounder	Questionnaire	Categorical	Baseline only
Employment	Potential confounder	Potential confounder	Questionnaire	Categorical	Baseline only
Education	Potential confounder	Potential confounder	Questionnaire	Categorical	Baseline only
Gender	Potential confounder	Potential confounder	Questionnaire	Binary	Baseline only
Non-injection drug use (in the last 3 months)	Potential confounder	Potential confounder	Questionnaire	Binary	Baseline only
History of injection drug use	Potential confounder	Potential confounder	Questionnaire	Binary	Baseline only
HIV stigma	Potential confounder	Potential confounder	Questionnaire	Binary	Baseline only
Social support	Potential confounder	Potential confounder	Questionnaire	Categorical	Baseline only
Intimate partner violence	Potential confounder	Potential confounder	Questionnaire	Binary	Baseline only

(*) Baseline, 3, 6 and 12 follow-up visits

(ɣ) Not applicable

4.2.3.4. Other covariates

Demographic characteristics of participants such as age, education, income, gender, and employment status, as well as drug use, social support, HIV stigma and intimate partner violence were assessed at baseline.

Table 4.2 shows a summary of key measures and time points when they were assessed.

4.2.3. Sample size and power

To calculate power, I chose the hypothesis of the effects of the interventions on depression and anxiety symptoms in Aim 2, since this is the central research question of this study. A meaningful effect size of 0.15 was chosen, as recommended for power analyses in behavioral sciences[208]. Based on results of correlations between repeated measures of anxiety and depression in the literature, I chose a value of 0.7 for such correlations in my study[209]. Using the GLIMMPSE software[210], I calculated the sample size needed to detect a standardized effect size of 0.15, assuming a correlation between repeated measures of depression and anxiety of 0.7, a 20% attrition rate and a type I error α=0.05. Based on these assumptions, the sample size needed to have an 80% power to detect such an effect size is 413 (or 138 people per group), which is smaller than the total sample size of the parent study. Based on preliminary data analysis, the real attrition rate in REDART was also much smaller, with the percentages of a missed visit ranging from 7-11%, depending on specific follow-up visit.

4.2.4. Analysis plan

4.2.5.1. Aim 1 and Sub-aim 1

Aim 1 evaluates the longitudinal association between mental health symptoms (depression and anxiety symptoms) and two HIV outcomes (viral suppression and complete ART

adherence) among ART clients with hazardous alcohol use. Statistical analyses for Aim 1 and Sub-aim 1 were done using SAS 9.4.

Means (Standard deviations (SD)) of continuous variables and proportions of categorical variables were reported. Generalized estimating equations (GEE) models were used to estimate the time-lagged associations between depression, anxiety symptoms and two HIV outcomes: viral suppression and complete ART adherence. I conducted lagged analyses of the association between mental health symptoms at a given visit and HIV outcomes at the following visit. In this paper, time refers to the time of outcome assessment, which included: 3-month, 6-month or 12-month follow-up visits. I estimated risk ratios (RR) of viral suppression and ART adherence associated with a 5-unit change in scores of depression and anxiety symptoms, as other studies have[211,212]. Since depression and anxiety symptoms were highly correlated in this sample, for each outcome, separate models with the same set of covariates were run for depression or anxiety symptoms as the main predictor. Since HIV outcomes in the sample were very common, the associations were explored using Poisson regression with robust variance estimation to avoid biases associated with inflated odds ratios[213]. Exchangeable covariance matrix between repeated measures was selected because it did not have convergence issues and had the smallest Quasi-likelihood Information Criterion (QIC)[214].

I assessed whether alcohol use modified the associations between mental health symptoms and HIV outcomes by adding interaction terms (e.g., depression symptoms × alcohol dependence) to the model. Similarly, the interactions between assessment time point and mental health symptoms were tested (e.g., depression symptoms × 3-month visit). Since the longitudinal effects of mental health symptoms on viral suppression may vary by baseline viral suppression, baseline viral suppression was also examined as a potential effect modifier. Interactions with

product terms not significantly different than 0 (at $p<0.05$ using the Wald test) were not included in the multivariable regression models. Significant modification effects were further explored by probing the associations of interest within stratum of the effect modifiers (controlling for confounders). Only covariates associated with the outcome at $p<0.1$ in the univariable models and meaningfully changed the main estimates of association (by more than 10%) were included in the final models [215,216]. Intervention exposure and time were kept in multivariable models regardless of statistical significance and meaningful change of the main estimates. Multiple imputation was used to accommodate missingness of depression, anxiety symptoms, viral suppression and adherence data at follow-ups[217,218].

4.2.5.2. Aim 2

Aim 2 describes the changes in depression and anxiety symptoms of ART clients who are hazardous drinkers in the parent trial over time, and assesses the impact of two evidence-based alcohol-reduction interventions on depression and anxiety symptoms among ART clients who are hazardous drinkers over time, comparing the effects of the two interventions to each other and to the control group. Statistical analyses for Aim 2 was done with SAS 9.4.

Means (standard deviations (SD)) of continuous variables and proportions of categorical variables at baseline, stratified by intervention arms, were reported. Descriptive data of absolute differences between scores of depression and anxiety symptoms at baseline and follow-up visits were presented, and percentage changes from baseline are calculated as the ratio of these differences over the baseline scores. GEE models with an unstructured covariance matrix were used to analyze intervention impacts on continuous scores of depression and anxiety over time, with baseline scores included as covariates. Time of assessment and intervention condition were included in the models as dummy coded variables. Interactions between time (follow-up visit)

and intervention condition were included to determine whether the association between intervention condition and the outcome varied over time. Based on the literature, baseline depression and anxiety symptoms, age, gender, education and employment were added to the final models to control for potential confounders [219-223]. Changes in depression and anxiety symptoms by intervention group as well as differences between the means of depression/anxiety symptoms between intervention groups at each follow-up visit were presented. Corresponding 95% confidence intervals (CIs) and p-values of inferential statistics were calculated.

I used multiple imputations to deal with missingness on depression and anxiety symptoms at follow-up; twenty imputed datasets were created, and pooled estimates were calculated using the MI and MIANALYZE procedures in SAS.

4.2.5.3. Aim 3

Aim 3 examines the mediating role of alcohol use in the pathway from the two alcohol-reduction interventions to depression and anxiety symptoms of participants at the last follow-up visit. Longitudinal structural equations models (SEM) were used for the analysis of the mediating role of alcohol use in the association between the intervention and depression/anxiety symptoms, since this technique allows for the assessment of different prospective pathways from the exposure variable to the mediator to the outcomes [224].

Two separate models were run for each of the main outcomes, depression and anxiety symptoms. Coefficients of each of the following pathways were estimated: from the interventions to alcohol use, measured as percentage of days abstinent from alcohol in the last 30 days (a paths); from percentage of days abstinent from alcohol in the last 30 days to depression and anxiety symptoms (b paths) and from the interventions to depression and anxiety symptoms (c' paths). I followed the recommendations of Goldsmith et al. for analyzing the mediation of

treatment effects using SEMs [225]. Even though lagged models can better ensure the chronological order between the mediator and outcome, models with contemporaneous paths may be more appropriate in some cases [225]. For example, if the time between the end of the intervention and the first assessment post-intervention is long enough for both the mediator and outcome to change, the potential effects of the mediator on the outcome could have already been observed at this assessment. Therefore, I estimated two different model specifications, one with lagged b-paths (alcohol use at one time point predicting mental health symptoms at the next time point), and one with contemporaneous b paths (alcohol use predicting mental health symptoms at the same time point) (Figure 4.3). The indirect effect via alcohol use was estimated as the product of a paths and b paths for the outcomes. In this study, indirect pathways from the interventions to the outcomes of depression and anxiety symptoms at 12 months (via alcohol use) included all pathways that went through at least one measure of alcohol use. All other pathways from the interventions to depression and anxiety symptoms at 12 months that only went through previous measures of depression and anxiety symptoms and did not go through any alcohol use measures were considered direct pathways. The total indirect effects and direct effects were calculated for the outcomes at 12 months by summing all corresponding effects at 12 months. Standard errors and 95% confidence intervals (CI) of indirect effects were calculated using the bootstrap procedure (n=5,000)[226]. At 12 months, the total indirect effect via alcohol use was considered significant (i.e., mediation by alcohol use was present) if the 95%CI of the total indirect effect did not include 0.

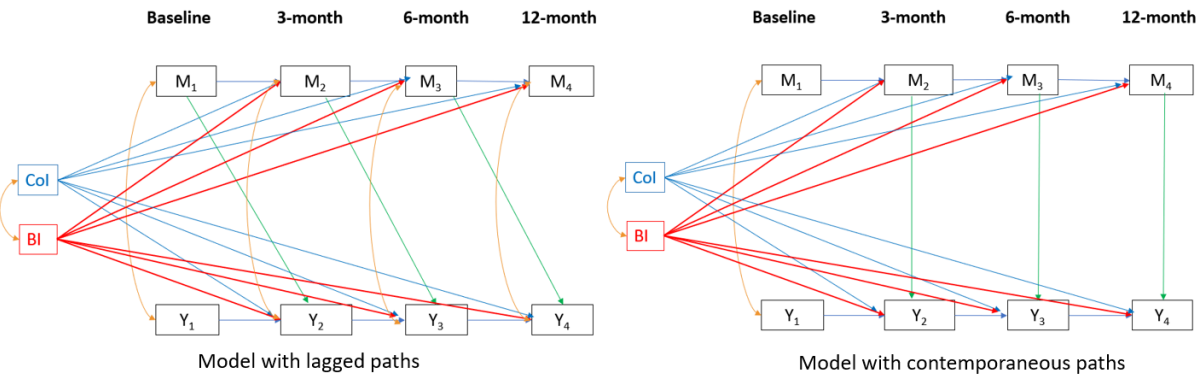


Figure 4.3: Longitudinal SEM models examining mediation through alcohol use

Note: CoI: Combined Intervention; BI: Brief Intervention; M: Mediator (alcohol use); Y: Outcome (depression or anxiety symptoms)

I first started with basic models having first-level autoregression paths (AR(1)) (measures of alcohol use and mental health symptoms were regressed on immediately preceding measures only) and no equality constraints (which meant the unstandardized estimates for two parameters of two different paths were not set to be equal). Level-two and level-three autoregression paths (AR(2) and AR(3), i.e., measures of alcohol use and mental health symptoms were regressed on previous two and three values) were then added if they led to significant improvement in model fit. Finally, to make the models more parsimonious, equality constraints of autoregression and b paths were tested and retained if models did not fit significantly worse. Based on the literature, age, gender, non-injection and injection drug use at baseline were chosen a priori and examined as potential confounders[227-233]. Finally, gender was added as a covariate in all models, since it was the only variable significantly correlated with both the mediators and outcomes at $p<0.05$. To further control for unmeasured confounders, AR pathways between measurements of the mediators and outcomes at different time points were included in all models. Moreover, alcohol use and depression/anxiety symptoms assessed at the same time point were allowed to covary, if a contemporaneous path did not already exist between them at that time point[225].

Comparative Fit Index (CFI) and Tucker–Lewis index (TLI) of 0.95 or greater and Root Mean Square Error of Approximation (RMSEA) of less than 0.06 were indicators of good model fit[234]. Even though I reported the chi-square index, it was not used as a fit criterion due to its tendency to reject models with large sample size [235]. Models with a smaller Bayesian Information Criterion (BIC) and Akaike's Information Criterion (AIC) were preferred, and a difference in BIC and AIC of 2 or more points was indicative of significant better fit[225,236]. To compare nested models and test equality constraint assumptions, the Likelihood ratio test and corresponding p-values were used [237]. All reported path coefficients, total overall effect, direct effect and indirect effect coefficients were unstandardized.

Descriptive and correlational statistical analyses were conducted using SAS 9.4. All SEM models were fitted with Mplus 8 using full information maximum likelihood (FIML). FIML also handled missing data, assuming data was missing at random, as recommended by Enders et al[238].

CHAPTER 5. THE LONGITUDINAL ASSOCIATION BETWEEN DEPRESSION, ANXIETY SYMPTOMS AND HIV OUTCOMES, AND THE MODIFYING EFFECT OF ALCOHOL DEPENDENCE AMONG ART CLIENTS WITH HAZARDOUS ALCOHOL USE IN VIETNAM

5.1. Introduction

People with HIV (PWH) are disproportionately affected by depression and anxiety disorders[3-5]. Indeed, PWH are 1.6 to 4 times more likely to be diagnosed with depression and anxiety disorders than HIV-negative individuals[2,39-43]. For example, a global systematic review reported a prevalence of depression among PWH ranging from 15% to 44%, depending on the region[239,240]. The presence of anxiety or depression symptoms among PWH has numerous implications for HIV outcomes. The Transactional Model of Stress and Coping suggests that the experience of stress can have a negative impact on physical health and functional status through direct physiological impacts on health or through indirect effects via maladaptive behaviors, such as non-adherence to medications[241]. Depression and anxiety symptoms among PWH are associated with poor viral load outcomes[5,25,80,81,83] and lower odds of achieving antiretroviral therapy (ART) adherence[6,71,72]. PWH with depression and anxiety symptoms generally have faster progression to AIDS and higher mortality rates[78,79,242-244].

Hazardous drinking is defined as the quantity and pattern of alcohol consumption that increases adverse health outcomes, while alcohol dependence - a higher level of alcohol use disorder – is defined as a strong desire to consume alcohol, difficulties in controlling its use, and persistent use despite harmful consequences[15,89]. An estimated 25% to 50% of PWH are hazardous drinkers[14,90,91], and about 10.6% of PWH had both depression symptoms and harmful levels of alcohol use[22]. PWH with hazardous alcohol use are even more vulnerable to mental

disorders than PWH without drinking issues[108], and they may have unique challenges that make abstinence difficult. For example, a study among PWH in Vietnam showed that participants were particularly susceptible to alcohol abstinence stigma, which was also associated with higher levels of alcohol use[245]. Therefore, it is essential to understand how depression and anxiety symptoms affect viral suppression and ART adherence among PWH with hazardous alcohol use. However, there is a dearth of research on the associations between depression, anxiety and HIV outcomes among this subgroup of PWH.

According to the Syndemics Theory, the co-existence and synergistic interaction of more than one adverse condition in a patient can produce worse health outcomes than each condition independently[164,166]. While mental health symptoms are independently associated with poorer HIV outcomes, alcohol use can also accelerate HIV progression through a number of mechanisms. High levels of alcohol use do not only negatively impact ART adherence and response to medication but can also lead to compromised liver function and liver diseases[101,103,113,232,246-249]. Therefore, mental health symptoms and high levels of alcohol use can substantially increase the risk of treatment failure among PWH[250]. The interrelationship between these comorbidities and HIV outcomes among PWH remains largely unknown. The understanding of how these comorbidities interact will shed light on the need for a more holistic approach to addressing psychological and substance use comorbidities for PWH.

In Vietnam, alcohol is accessible and affordable, and excessive alcohol consumption is common during social and business gatherings [140,143]. A study among 1016 PWH in Vietnam found that 30.1% of PWH had hazardous alcohol use[137]. Vietnamese PWH are also commonly affected by mental health disorders such as depression and anxiety[145,146]. Using data from a randomized controlled trial of two alcohol reduction interventions among PWH with hazardous

alcohol use in Vietnam, I aim to (1) evaluate the longitudinal association between mental health symptoms (depression and anxiety symptoms) and two HIV outcomes (viral suppression and complete ART adherence) among ART clients with hazardous alcohol use in Vietnam; and (2) determine whether alcohol dependence modifies the longitudinal association between depression, anxiety symptoms and HIV outcomes (conceptual model shown in Appendix A, Figure A1).

5.2. Methods

5.2.1. Study design and study population

This research is a secondary data analysis of the parent study, *Reducing Hazardous Alcohol Use & HIV Viral Load: A Randomized Controlled Trial in Antiretroviral Treatment (ART) Clinics in Vietnam* [REDART; NCT02720237]. REDART is a three-arm RCT conducted from March 2016 to May 2018 among ART clinic patients with hazardous alcohol use in Thai Nguyen - a mountainous, multi-ethnic province located in Northeast Vietnam[251]. Mirroring Vietnam's broader epidemic, HIV transmission in Thai Nguyen is primarily driven by injection drug use, with an HIV prevalence among people who inject drugs of 31.2%[136].

The main goal of the parent study was to understand the relative effectiveness of two interventions based on Motivational Enhancement Therapy (MET) and Cognitive Behavioral Therapy (CBT) in improving alcohol- and HIV-related outcomes[251]. Four hundred and forty PWH with hazardous alcohol use were randomly assigned to receive either a combined intervention, a brief intervention or a standard of care assessment control. Participants were recruited from 6 ART community clinics and 1 ART hospital clinic. The World Health Organization (WHO) Alcohol Use Disorders Identification Test-Concise (AUDIT-C) survey, which had been utilized in previous studies in Vietnam[137,252-255], was used to assess eligibility[33]. Men and women who scored ≥ 4 (men) or ≥ 3 (women) on the AUDIT-C were considered

eligible[33]. Additional inclusion criteria were: 1) being a current ART client; 2) being ≥ 18 years of age; and 3) planning to reside in Thai Nguyen for the next 24 months. Exclusion criteria were: 1) inability to provide informed consent due to cognitive impairment or having threatening behavior (study staff assessed sobriety); 2) unwilling to provide locator information; or 3) currently participating in other HIV, drug use or alcohol program, study, or intervention. Survey data, along with viral load data were collected at baseline, 3 months, 6 months and 12 months after the intervention. All questionnaires were administered in Vietnamese. The study was reviewed and approved by the University of North Carolina at Chapel Hill's Institutional Review Board (IRB) and the IRB at the Thai Nguyen Center for Preventive Medicine.

The combined and brief interventions were associated with significantly improvement of the primary outcome - percent days abstinent, compared to standard of care group at 12 months. Viral suppression (<20 copies of HIV-1 RNA per milliliter) at 12 months was also higher after the brief intervention than the standard of care.

5.2.2. Measurements

5.2.2.1. Depression and anxiety symptoms

At all visits, depression symptoms were assessed with the Patient Health Questionnaire-9 (PHQ-9) scale[194] and anxiety symptoms were assessed with the Generalized Anxiety Disorder-7 (GAD-7) scale[203,256]. In Vietnam, the PHQ-9 scale has shown good convergent validity, construct validity as well as reliability[257], and has been used for a range of populations, including PWH[149,195,196]. Nine items assess how often depression symptoms including loss of interest or pleasure in doing things or feeling down or depressed occurred in the last 2 weeks. The GAD-7 scale has not been formally validated in Vietnam but has been used in different Vietnamese populations to measure anxiety[199,200]. This scale has 7 items that evaluate the frequency of

symptoms such as feeling nervous, anxious, or on edge or not being able to stop or control worrying. For both the PHQ-9 and GAD-7, a cut-off score of 5 can be interpreted as having mild levels of symptoms that are consistent with depression and anxiety, respectively[258,259]. The maximum scores for depression and anxiety symptoms were 27 and 21, respectively. Since classifying continuous data into binary data can result in a loss of power and binary data are less sensitive to change[204], the original continuous scores of depression and anxiety symptoms were used in this study. Depression and anxiety symptoms were rescaled so that the reported estimates of association reflect the change in outcome associated with a 5-unit change in the continuously measured PHQ-9 or GAD-7 score. I performed this rescaling because a 1-unit change in each score is not clinically meaningful, whereas a 5-unit change is considered potentially clinically significant, implying that a participant has moved from one level of severity to the next [260,261]. This rescaling method has been used in other studies using continuous measures of depression and anxiety symptoms[211,212].

5.2.2.2. Alcohol dependence

Alcohol dependence was evaluated with the Mini International Neuropsychiatric Interview (MINI) questionnaire[205] – a 7-item structured diagnostic psychiatric interview in which endorsing 3 or more items indicates alcohol dependence[262].

5.2.2.3. Viral suppression and ART adherence

Viral load was measured by HIV-1 ribonucleic acid (RNA) levels using the in vitro nucleic acid amplification test (COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test). Viral suppression was defined as having less than 20 copies/ml. Complete ART adherence (self-reported) was defined as no missed pills in the past 3 months. Both HIV viral load and self-reported adherence were measured at baseline, 3, 6 and 12-month follow-ups. Since ART

adherence is subject to social desirability bias[263], viral suppression was considered the primary outcome of interest in this study.

5.2.2.4. Demographics and other covariates

Standard demographics were collected at baseline (e.g. age, marital status, education, employment). Based on the literature, the following covariates were chosen a priori as potential confounders: age, sex, education, marital status, employment, alcohol dependence, non-injection drug use, injection drug use, social support, HIV stigma and intimate partner violence [83,233,264-270]. Participants were asked if they had used any types of non-injection drugs (including heroin, methamphetamines, etc.) in the last 3 months and if they had ever injected drugs in the past. Social support was measured with a 5-question modified version of the Medical Outcomes Study Social Support Instrument[271] used previously among PWH in Vietnam[272]. Based on the distribution of the social support score at baseline, the social support level was classified into 4 quartiles. To evaluate HIV stigma, participants were asked to state their levels of agreement with four statements indicating internalized, experienced or anticipated HIV stigma. They were classified as having HIV stigma if they reported any level of agreement with any of the four statements. Participants were classified as having ever experienced intimate partner violence if they had ever been a victim of physical, emotional or sexual abuse in an intimate relationship.

5.2.3. Statistical analysis

Means (Standard deviations (SD)) of continuous variables and proportions of categorical variables were reported. Generalized estimating equations (GEE) models were used to estimate the time-lagged associations between depression, anxiety symptoms and two HIV outcomes: viral suppression and complete ART adherence. I conducted lagged analyses of the association between mental health symptoms at a given visit and HIV outcomes at the following visit. In this

paper, time refers to the time of outcome assessment, which included: 3-month, 6-month or 12-month follow-up visits. I estimated risk ratios (RR) of viral suppression and ART adherence associated with a 5-unit change in scores of depression and anxiety symptoms, as other studies have[211,212]. Since depression and anxiety symptoms were highly correlated in this sample, for each outcome, separate models with the same set of covariates were run for depression or anxiety symptoms as the main predictor. Since HIV outcomes in the sample were very common (Table 5.1), the associations were explored using Poisson regression with robust variance estimation to avoid biases associated with inflated odds ratios[213]. Exchangeable covariance matrix between repeated measures was selected because it did not have convergence issues and had the smallest Quasi-likelihood Information Criterion (QIC)[214].

I assessed whether alcohol use modified the associations between mental health symptoms and HIV outcomes by adding interaction terms (e.g., depression symptoms × alcohol dependence) to the model. Similarly, the interactions between assessment time point and mental health symptoms were tested (e.g., depression symptoms × 3-month visit). Since the longitudinal effects of mental health symptoms on viral suppression may vary by baseline viral suppression, baseline viral suppression was also examined as a potential effect modifier. Interactions with product terms not significantly different than 0 (at $p<0.05$ using the Wald test) were not included in the multivariable regression models. Significant modification effects were further explored by probing the associations of interest within stratum of the effect modifiers (controlling for confounders). Only covariates associated with the outcome at $p<0.1$ in the univariable models and meaningfully changed the main estimates of association (by more than 10%) were included in the final models[215,216]. Intervention exposure and time were kept in multivariable models regardless of statistical significance and meaningful change of the main estimates. Multiple

imputation was used to accommodate missingness of depression, anxiety symptoms, viral suppression and adherence data at follow-ups[217,218].

Statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

5.3. Results

5.3.1. Sample characteristics at baseline

The mean age of enrolled participants (n=440) was 40.2 years old (SD=5.8) (Table 5.1). Almost all participants were male (96.8%), and 85% had at least some secondary school education. More than two thirds (69.3%) were married, and 81.1% were employed at baseline. Most participants had a history of injection drug use (80.9%), and 39.1% had used non-injection drugs in the past 3 months. Alcohol dependence based on the MINI score was identified among 21.1% of participants. More than half had ever experienced HIV stigma (61.4%), and 37.5% had ever experienced intimate partner violence. Mean social support score was 63.3 (SD=29.3, scale 0 to 100).

At baseline, 84.1% were virally suppressed and 76.4% had not missed an ART pill in the last 3 months. There was no difference in depression symptoms between participants with and without viral suppression at baseline. A slightly lower score for anxiety symptoms was observed among those with viral suppression (Table 5.1). Those who completely adhered to their ART regimen at baseline had lower depression and anxiety symptoms scores, compared to those without complete adherence.

Table 5.1. Participants' baseline characteristics, stratified by viral suppression and ART adherence at baseline

Characteristics N (%)	Complete ART adherence at baseline		Viral suppression at baseline		Total (N=440)
	Yes (N=334)	*No (N=103)*	*Yes (N=370)*	*No (N=70)*	
Age (years) (mean±SD)	40.8 ± 5.6	38.2 ± 5.8	40.3 ± 5.6	39.9 ± 6.6	40.2 ± 5.8
Male	322 (96.4)	101 (98.1)	361 (97.6)	65 (92.9)	426 (96.8)
Education					
Primary school or less	51 (15.3)	14 (13.6)	55 (14.9)	11 (15.7)	66 (15.0)
Some secondary school	191 (57.2)	53 (51.5)	201 (54.3)	45 (64.3)	246 (55.9)
Some high school	66 (19.8)	20 (19.4)	76 (20.5)	10 (14.3)	86 (19.6)
Some technical training, college or university	26 (7.8)	16 (15.5)	38 (10.3)	4 (5.7)	42 (9.6)
Marital status					
Not married	54 (16.2)	25 (24.3)	67 (18.1)	12 (17.1)	79 (18.0)
Married	245 (73.4)	57 (55.3)	261 (70.5)	44 (62.9)	305 (69.3)
Widowed, divorced or separated	35 (10.5)	21 (20.4)	42 (11.4)	14 (20.0)	56 (12.7)
Employment (Yes)	273 (81.2)	81 (78.6)	297 (80.3)	60 (85.7)	357 (81.1)
History of injection drug use (Yes)	267 (80.0)	87 (84.5)	301 (81.4)	55 (78.6)	356 (80.9)
Non-injection drug use in the past 3-month (Yes)	125 (37.4)	46 (44.7)	145 (39.2)	27 (38.6)	172 (39.1)
Alcohol dependence (Yes)	55 (16.5)	36 (35.0)	82 (22.2)	11 (15.7)	93 (21.1)
Ever experienced, internalized or anticipated HIV stigma (Yes)	200 (59.9)	68 (66.0)	230 (62.2)	40 (57.1)	270 (61.4)
Ever experienced intimate partner violence (Yes)(*)	111 (33.5)	51 (50.5)	140 (38.3)	23 (33.3)	163 (37.5)
Social support (mean ± SD)	64.6 ± 28.9	61.1 ± 29.6	64.4 ± 29.2	60.7 ± 28.6	63.3 ± 29.27
Depression symptoms (mean ± SD)	2.6 ± 3.5	3.8 ± 4.2	2.9 ± 3.7	2.9 ± 3.9	2.9 ± 3.70
Anxiety symptoms (mean ± SD)	1.3 ± 2.5	2.4 ± 3.6	1.5 ± 2.8	1.9 ± 3.1	1.6 ± 2.85

(*) Five participants had missing data on intimate partner violence at baseline

Note: ART: antiretroviral therapy; SD: standard deviation

5.3.2. Distribution of depression, anxiety symptoms and HIV outcomes over time

Figure 5.1 shows changes in mental health symptoms, viral suppression and ART adherence of the whole sample over time. There is a decrease in observed depression and anxiety symptoms from baseline to 12-month follow-up. There were no significant changes in viral

suppression over time, while complete ART adherence increased from 76.4% at baseline to 84.8% at the last follow-up.

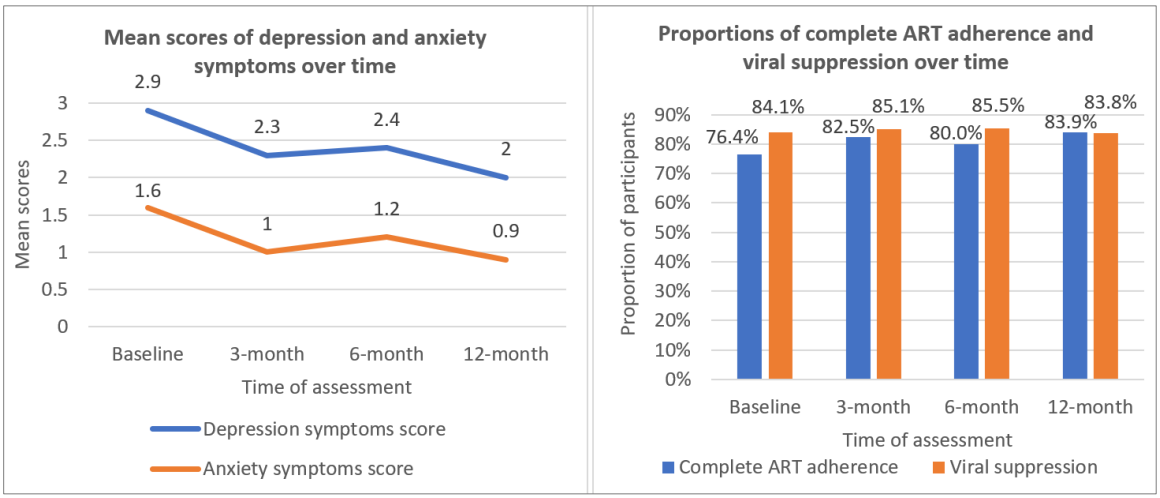


Figure 5.1. Changes in depression, anxiety symptoms, viral suppression and complete ART adherence of the sample over time

5.3.3. Associations between depression, anxiety symptoms and HIV outcomes

Overall, there were no associations between mental health symptoms and viral suppression. However, a 5-point increase in depression or anxiety symptoms score was associated with a lower probability of complete ART adherence at the next visit (depression symptoms: adjusted risk ratio (aRR)=0.95; 95% CI: 0.91-0.99; anxiety symptoms: aRR=0.93; 85% CI: 0.88-0.99) (Table 5.2).

There was a significant effect modification by time, and the strength and significance of the associations between anxiety symptoms and HIV outcomes varied across study time points. Estimates of the full models with p-values of interaction terms are presented in Appendix A, Table A1. When being stratified by time, both baseline depression and anxiety symptoms were associated with a lower probability of complete ART adherence at 3 months (depression symptoms: aRR=0.90; 95%CI: 0.84-0.97; anxiety symptoms: aRR=0.87; 85%CI: 0.79-0.96), though no association was seen with viral suppression. At subsequent follow-up visits, there was

no association between symptoms of depression and anxiety with either viral suppression or complete ART adherence, except for a signal of higher viral suppression at 12 months associated with a 5-point increase in anxiety symptoms at 6 months (aRR=1.09; 95%CI 1.02-1.17) (Table 5.3). Baseline viral suppression was not a significant modifier of the associations between depression, anxiety and viral suppression (Appendix A, Tables A2.1 and A2.2).

Table 5.2. Associations between depression, anxiety symptoms and HIV outcomes at the next visit[1]

	Viral supression[2]			ART adherence[3]		
	aRR	**95%CI**	**p-values**	**aRR**	**95%CI**	**p-values**
Depression symptoms	1.00	0.96-1.03	0.94	0.95	0.91-0.99	0.03
Anxiety symptoms	1.00	0.95-1.05	0.98	0.93	0.88-0.99	0.02

[1]Each multivariable model has only one mental health predictor, either depression symptoms or anxiety symptoms; models with the same outcome have the same set of covariates. aRRs were associated with a 5-point increase in scores of depression or anxiety symptoms at the previous time point
[2]Models predicting viral suppression controlled for age, viral suppression at baseline, intervention exposure and time
[3]Models predicting adherence controlled for marital status, alcohol dependence at baseline, adherence at baseline, intervention exposure and time
Note: ART: antiretroviral therapy; aRR: adjusted risk ratio; CI: confidence interval

Table 5.3. Associations between depression, anxiety symptoms and HIV outcomes at the next visit, stratified by time of outcome assessment[1]

Time of outcome assessment	**Models predicting viral suppression[2]**			**Models predicting complete ART adherence[3]**		
	aRR	**95%CI**	**p-values**	**aRR**	**95%CI**	**p-values**
Main predictor: Depression symptoms						
At 3 months	0.99	0.94-1.04	0.66	0.90	0.84-0.97	0.005
At 6 months	0.97	0.91-1.03	0.31	0.96	0.89-1.03	0.28
At 12 months	1.05	1.00-1.10	0.09	1.01	0.94-1.09	0.69
Main predictor: Anxiety symptoms						
At 3 months	0.96	0.89-1.03	0.30	0.87	0.79-0.96	0.005
At 6 months	0.96	0.86-1.07	0.50	0.90	0.79-1.03	0.14
At 12 months	1.09	1.02-1.17	0.02	1.04	0.96-1.13	0.36

[1]Each multivariable model has only one mental health predictor, either depression symptoms or anxiety symptoms at the previous time point. Models with the same outcome have the same set of covariates. Time presented in the first column is the time of assessment of viral suppression and ART adherence. aRRs were associated with a 5-point increase in scores of depression or anxiety symptoms at the previous time point.
*[2]Models predicting viral suppression control for age, viral suppression at baseline, intervention exposure, time, interaction of time*depression/anxiety symptoms*
*[3]Models predicting adherence control for marital status, alcohol dependence at baseline, adherence at baseline, intervention exposure, time, interaction of time*depression/anxiety symptoms*
Note: ART: antiretroviral therapy; aRR: adjusted risk ratio; CI: confidence interval

5.3.4. Possible effect modification role of alcohol dependence

Alcohol dependence at baseline significantly modified the association between anxiety symptoms and complete ART adherence (p-value for interaction term=0.02). Anxiety symptoms at baseline and lower probability of complete adherence at 3 months were more strongly related among participants with alcohol dependence, compared to those without (Table 5.4). Anxiety symptoms only predicted poor adherence at 6 months among those with alcohol dependence. At 12 months, there was no association between anxiety at the previous time point and adherence for all participants. The interactions between alcohol dependence and mental health symptoms in the remaining associations (depression predicting both HIV outcomes and anxiety predicting viral suppression) were not significant at $p<0.05$ and were not further explored.

Table 5.4. Associations between anxiety symptoms and complete ART adherence at the next visit, stratified by alcohol dependence and time since baseline

Time of outcome assessment	aRR[1]	95%CI	p-values
At 3-month visit			
Alcohol dependence	0.80	0.68-0.94	0.008
No alcohol dependence	0.90	0.82-0.99	0.04
At 6-month visit			
Alcohol dependence	0.82	0.68-0.99	0.05
No alcohol dependence	0.93	0.82-1.06	0.33
At 12-month visit			
Alcohol dependence	0.95	0.81-1.12	0.57
No alcohol dependence	1.08	1.00-1.17	0.08

[1]*Models controlling for marital status, alcohol dependence at baseline, adherence at baseline, intervention exposure, time, interaction of time* anxiety symptoms, interaction of alcohol dependence*anxiety symptoms. aRRs were associated with 5-point increase in scores of anxiety symptoms at the previous time point*
Note: aRR: adjusted risk ratio; CI: confidence interval

5.4. Discussion

Among a sample of 440 ART clients with hazardous alcohol use, I did not find an overall effect of depression and anxiety symptoms on viral suppression, but observed a decreased probability of complete ART adherence associated with increased depression and anxiety symptoms. The magnitude and significance of the associations varied by the time of outcome

assessment. Negative effects of anxiety symptoms on ART adherence were significantly worse among participants with alcohol dependence at baseline, compared to those without alcohol dependence.

While there was no effect of mental health symptoms on viral suppression when all time points were taken into account, I found that anxiety symptoms were associated with a small increase in the probability of viral suppression at the last follow-up. This was an unexpected finding, although one study among PWH in Russia also reported that greater state of anxiety was positively associated with better adherence[83]. Previous studies reported a Hawthorne effect, which refers to the alteration of behavior of subjects due to awareness of being observed in a study [273,274]. Moreover, an inverted U-shaped association between arousal, anxiety, and performance[275,276] has been demonstrated. By participating in multiple rounds of interviews, participants with milder anxiety symptoms might become more aware of and worried about their health's status, and therefore more motivated to take action to improve their overall health.

Our results are similar to other studies that examined the association between mental health symptoms and ART adherence in the general population of PWH[6,72]. However, the magnitudes of the associations in this study were smaller than those reported by previous studies. Participants in this sample had a high proportion of viral suppression and ART adherence at baseline, which leaves fewer opportunities for enhancement of HIV outcomes. Due to the Hawthorne effect mentioned above, being a participant in REDART over time might have also attenuated the effects of mental health problems on adherence and viral suppression to some extent, regardless of which intervention arm the participant belonged to. This might help explain why stratification by time only showed significant associations between mental health symptoms and ART adherence at the 3-month visit.

I also found that the negative effects of anxiety symptoms on ART adherence at earlier time points were modified by alcohol dependence such that the associations appeared to be stronger among those with alcohol dependence. Previous studies among PWH reported that higher number of syndemic conditions was associated with higher HIV viral load and lower ART adherence[114,171], although the authors did not examine the specific interaction of alcohol use and mental health symptoms. PWH can use alcohol as a coping strategy, which may help improve mood to an extent[143]. However, since hazardous alcohol use independently decreased ART adherence[16,98], high levels of alcohol use such as alcohol dependence among PWH with anxiety symptoms may pose greater challenges than benefits to adherence.

Our analyses have several limitations. First, self-reported measures of adherence are more likely to produce measurement errors, as compared to objective measures such as electronic medication packaging devices[263]. In order to minimize this limitation, I also analyzed the associations between mental health symptoms and HIV viral suppression - a biological outcome not subject to such biases. Second, this study was not immune to loss to follow-up - a common issue affecting longitudinal analyses. We had missing data for key predictors and outcomes at the follow-up visits, ranging from 7-12% (Appendix A, Table A3). In this study I used multiple imputation to impute missing values of depression, anxiety symptoms, viral suppression and adherence for the sample, as recommended for GEE analyses of longitudinal data[217,218]. Third, this was not a random sample of ART clients. The majority of the participants were men and had a history of injection drug use. HIV transmission in Thai Nguyen is primarily driven by injection drug use[136] – a behavior more commonly seen among men in Vietnam[277,278]. Other studies among PWH in Vietnam also reported overwhelming proportions of participants being male with drug use behaviors[137,254]. Finally, in this study I reported aRRs associated with a

5-unit change in depression and anxiety symptoms. I acknowledge that there are alternative ways to analyze PHQ-9 and GAD-7 scores, which might result in different estimates of the associations between mental health symptoms and HIV outcomes than ours.

Our findings suggest that increased depression or anxiety symptoms over time are associated with decreased ART adherence among PWH with hazardous alcohol use, and support a modifying effect of alcohol dependence on the association between anxiety symptoms and ART adherence in this group. I recommend that future interventions aim to raise awareness about mental health problems among PWH, especially those with alcohol use disorders. Mental health services such as screening, counseling or medication treatment are also imperative to improve HIV outcomes for PWH with hazardous alcohol use. These mental health services can be integrated into alcohol use interventions or into existing HIV primary care clinics in Vietnam. It is also important that these interventions are tested for efficacy and cost-effectiveness in low-resource settings such as Vietnam.

5.5. Conclusions

Depression and anxiety symptoms had no overall effect on viral suppression, although anxiety symptoms at 6 months were associated with a mild increase in the probability of viral suppression at 12 months. Increased depression and anxiety symptoms were associated with a lower probability of complete ART adherence, and participants with both alcohol dependence and anxiety symptoms had lowest adherence. Interventions focusing on mental health care for PWH with hazardous alcohol use are much needed, and optimal models integrating mental health care and alcohol reduction should be implemented and tested in HIV primary care clinics in low-resource settings.

CHAPTER 6. EFFECTS OF TWO ALCOHOL REDUCTION INTERVENTIONS ON DEPRESSION AND ANXIETY SYMPTOMS OF ART CLIENTS IN VIETNAM

6.1. Introduction

Depression and anxiety disorders among people with HIV (PWH) have risen in the last three decades [3,61]. In fact, PWH are 1.6 to 4 times more likely to be diagnosed with depression and anxiety disorders than comparable HIV-negative individuals[2,39-43]. Mental health disorders such as depression and anxiety are significantly associated with poor antiretroviral therapy (ART) adherence, lower chances of achieving undetectable viral load and higher mortality rates[6,12,71,72,77-79]. Therefore, reducing depression and anxiety symptoms among PWH can play a critical role in improving HIV outcomes and overall health for this population.

Hazardous alcohol use and dependence is another widespread problem among PWH. Between a quarter to almost half of PWH reported hazardous alcohol use[14,90,91], which is defined as a quantity or pattern of alcohol consumption that increases adverse health outcomes for an individual[15]. Mental disorders and hazardous drinking often co-exist among PWH[21-24,105], and these co-morbidities can interact with each other to exacerbate negative HIV-related outcomes, such as ART adherence and HIV viral load [114,116,117,171]. In Vietnam, the prevalence of hazardous drinking among PWH on ART is 30%[137]. PWH in Vietnam also face multiple cultural and contextual barriers at different levels to reducing alcohol use, such as high affordability and availability and social pressures to drink[143,144].

Motivational Enhancement Therapy (MET) and Cognitive Behavioral Therapy (CBT) are two common behavioral intervention approaches that have been used to reduce alcohol use

among PWH with hazardous/heavy alcohol use[28-30]. MET is a client-centered counseling style based on Motivational Interviewing (MI) that aims to explore and resolve clients' ambivalent feelings about changing their behaviors and induce motivation for change, with personalized feedback on the levels of alcohol use and the impacts on physical and mental functioning to enhance motivation[119]. CBT, on the other hand, primarily focuses on skill-building for clients to cope with negative emotions and dysfunctional behaviors[120]. Alcohol reduction interventions drawing on both MET/MI and CBT have successfully reduced alcohol consumption, increased condom use, and improved ART adherence among PWH [28,30,121]. However, little is known about the impact of MET- and CBT-based alcohol interventions on the mental health of PWH. There are at least two ways through which alcohol interventions might impact depression and anxiety symptoms of participants. First, alcohol interventions can either directly influence depression and anxiety symptoms through the improvements of coping skills, motivation to change, and perceived social support, which in turn may reduce depression and anxiety[279-283]. Second, high levels of alcohol consumption are associated with increased risks of depression and anxiety, either through the social consequences of excessive drinking such as unemployment or relationship problems, or through changes in neurotransmitters due to alcohol use disorders[108,284-286]. Therefore, alcohol interventions have the potential to impact mental health indirectly through the reduction of alcohol use.

Accordingly, I undertook a secondary data analysis of a three-arm randomized controlled trial of two different alcohol reduction interventions among PWH in Vietnam to examine whether the interventions affected depression and anxiety symptoms over follow-up[251]. In this study, I aim to (1) describe the changes in depression and anxiety symptoms of ART clients who are hazardous drinkers over time and (2) assess the impact of two evidence-based alcohol-

reduction interventions on depression and anxiety symptoms at 3, 6, and 12 months post-intervention, comparing the effects of the two interventions to each other and to the standard of care (SOC) group.

6.2. Methods

6.2.1. Study design and setting

The study "*Reducing Hazardous Alcohol Use & HIV Viral Load: A Randomized Controlled Trial in Antiretroviral Treatment (ART) Clinics in Vietnam"* (REDART) was conducted from March 2016 to June 2018 among ART clinic patients with hazardous alcohol use in Thai Nguyen province - a mountainous, multi-ethnic province in Northeast Vietnam where HIV transmission is primarily driven by injection drug use[136]. The study aimed to evaluate the effects of a combined intervention and a brief intervention drawing from MET and CBT on alcohol use and viral suppression. Both interventions significantly increased the percentage of days abstinent at 12 months, and the participants in the brief intervention arm also had significantly higher viral suppression at 12 months, compared to the SOC[251].

ART clients at 7 HIV clinics in Thai Nguyen were enrolled if they met the criteria for hazardous alcohol use: scoring ≥ 4 (men) or ≥ 3 (women) on the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) questionnaire[33]. Additional inclusion criteria were: 1) ≥ 18 years of age and 2) plan to reside in Thai Nguyen for the next 24 months. Exclusion criteria included: 1) inability to provide informed consent due to cognitive impairment or having threatening behavior (study staff assessed sobriety); 2) unwilling to provide locator information; or 3) currently participating in other HIV, drug use or alcohol program, study, or intervention. Participants were also excluded if they scored a point of 10 or more on the Clinical Institute Withdrawal Assessment[287], which evaluated the risks of alcohol withdrawal. Eligible ART

clients were enrolled and randomized to receive either a combined, brief intervention or SOC. All participants had 3, 6, and 12-month follow-up assessments (Figure 6.1).

6.2.2. Interventions

The combined intervention was comprised of six individual face-to-face sessions (45-60 minutes each session) and three optional group sessions, with individual sessions occurring approximately one week apart. The combined intervention combined aspects from both MET and CBT. It used a client-centered, motivational interviewing approach and focused on developing positive thoughts and skill-building for alcohol use behavior change, including drinking refusal skills and coping skills to manage cravings and triggers. Counselors also provided personalized feedback on drinking patterns and harmful effects of drinking with patients. The brief intervention also combined elements from both CBT and MET, but condensed them into a 1- or 2-session format [193]. This intervention comprised two individual face-to-face sessions (30-45 minutes each session) and two individual booster phone sessions (10-15 minutes each session). The face-to-face sessions occurred approximately one month apart, and a phone session occurred 2-3 weeks after each face-to-face session. Contents of the brief intervention sessions also included review of drinking patterns, harmful effects of drinking and alcohol use behavior change strategies. The cultural adaption of the interventions has been described in detail previously [193]. Participants randomized to the SOC arm received standard messages from providers to drink less alcohol and referrals to alcohol abuse and infectious diseases treatment (Hepatitis B, Hepatitis C and other sexually transmitted diseases) at a general hospital in Thai Nguyen.

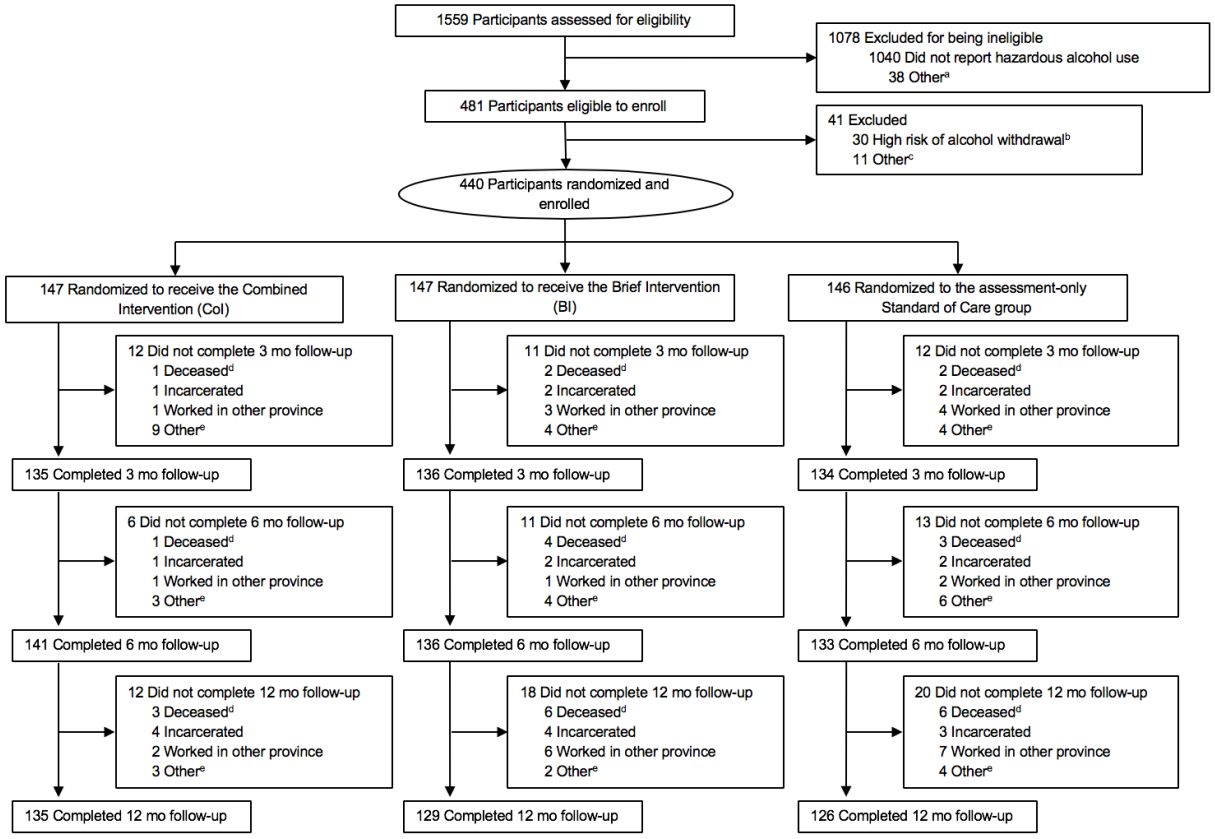
6.2.3. Measurements

A survey was administered at each visit and included items on depression, anxiety symptoms, alcohol use and other sociodemographic characteristics such as age, education, marital status and employment.

6.2.3.1. Depression and anxiety symptoms

The Patient Health Questionnaire-9 (PHQ-9), which has been well validated in Vietnam, was used to assess depression symptoms[149,194-196]. The nine items in the scale evaluate how often the respondent has experienced depression symptoms in the last 2 weeks. Examples of symptoms included *"Little interest or pleasure in doing things"* or *"Feeling down, depressed or hopeless".* The maximum score for depression symptoms is 27, and a score of 5, 10 and 20 or more is indicative of mild, moderate and severe depression symptoms [194].

Anxiety symptoms were assessed with the Generalized Anxiety Disorder-7 (GAD-7) scale. The GAD-7 has also been validated among PWH and has been used in Vietnamese populations to measure anxiety[197-200]. The GAD-7 evaluates the frequency of seven anxiety symptoms such as "*feeling nervous, anxious, or on edge*", "*not being able to stop or control worrying*" or having "*trouble relaxing*" in the last 2 weeks. Similar to the PHQ-9, participants scoring 5 points or more on the scale are considered to have at least mild anxiety symptoms[203]. The range of the GAD-7 score is from 0 to 21.



[a]*Including currently participating in another HIV, drug use, or alcohol program; plan to move from province in next 24 months; unwilling to adhere to program.*

[b]*High risk of alcohol withdrawal defined as Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA) score ≥10. Participants could re-screen if they returned and had CIWA score <10.*

[c]*Including did not complete baseline assessment; did not complete baseline laboratory testing; other.*

[d]*Number of deaths is cumulative.*

[e]*Including could not be contacted; refused to return; other.*

Note: This trial flowchart has been presented in previously published works from the parent study [251]. Mo=month.

Figure 6.1. REDART trial flowchart

6.2.3.2. Alcohol use

Since all participants were classified as having hazardous alcohol use at baseline, alcohol dependence was evaluated with the Mini International Neuropsychiatric Interview (MINI)

questionnaire[205] – a 7-item structured diagnostic psychiatric interview in which endorsing 3 or more items indicates alcohol dependence[262].

6.2.4. Statistical analyses

Means (standard deviations (SD)) of continuous variables and proportions of categorical variables at baseline, stratified by intervention arms, were reported. Descriptive data of absolute differences between scores of depression and anxiety symptoms at baseline and follow-up visits were presented, and percentage changes from baseline are calculated as the ratio of these differences over the baseline scores. Generalized estimating equations (GEE) models with an unstructured covariance matrix were used to analyze intervention impacts on continuous scores of depression and anxiety symptoms over time, with baseline scores included as covariates. Time of assessment and intervention condition were included in the models as dummy coded variables. Interactions between time (follow-up visit) and intervention condition were included to determine whether the association between intervention condition and the outcome varied over time. Based on the literature, baseline depression and anxiety symptoms, age, gender, education and employment were added in the final models to control for potential confounders[219-223]. Changes in depression and anxiety symptoms by intervention group as well as differences between the means of depression/anxiety symptoms between intervention groups at each follow-up visit were presented. Corresponding 95% confidence intervals (CIs) and p-values of inferential statistics were calculated.

At the 3-month, 6-month, and 12-month follow-ups, 35 (8%), 30 (7%), and 50 (11%) participants had a missed visit, respectively. Missingness at 6-month was associated with both higher depression and anxiety scores at baseline, while missingness at 12-month was associated with only higher depression scores at baseline. I used multiple imputations to deal with

missingness on depression and anxiety symptoms at follow-up; twenty imputed datasets were created, and pooled estimates were calculated using the MI and MIANALYZE procedures in SAS.

All statistical analyses were conducted with SAS 9.4 (SAS Institute, Inc., Cary, North Carolina). The UNC IRB and the local IRB at the Thai Nguyen Center for Preventive Medicine provided ethics review and approval for the study.

6.3. Results

Among 1559 ART clients who were screened for eligibility, 440 participants were enrolled in the study. At baseline, the mean age of participants was 39.6 (standard deviation (SD)=5.8). The majority of participants were male (96.8%), married (69.3%), and employed either full-time or part-time (81.1%).

Eighty-five percent of participants had at least some secondary education. The mean number of drinking days in the last 30 days was 18.1 days (SD=10.0), and more than 20% of participants had alcohol dependence at baseline. The mean duration of time since ART initiation was 5.5 years (SD=3.2). The percentage of participants having at least mild level of depression and anxiety symptoms at baseline was 25.1% and 16.1%, respectively. No significant differences in these characteristics across arms were observed (Table 6.1).

Table 6.1. Participants' baseline characteristics, stratified by intervention arms

Characteristics N (%)	**Brief intervention (N=147)**	**Combined intervention (N=147)**	**Standard of care (N=146)**	**Total (N=440)**	***p-values[1]***
Age (years) (Mean (SD))	39.8 (5.6)	40.5 (5.8)	40.3 (5.9)	40.2 (5.8)	*0.63*
Male	140 (95.2)	145 (98.6)	141 (96.6)	426 (96.8)	*0.25*
Education					*0.30*
Primary school or less	26 (17.7)	23 (15.7)	17 (11.6)	66 (15.0)	
Some secondary school	74 (50.3)	83 (56.5)	89 (61.0)	246 (55.9)	
Some high school	30 (20.4)	32 (21.8)	24 (16.4)	86 (19.6)	
Some technical training, college or university	17 (11.6)	9 (12.9)	16 (11.0)	42 (9.6)	
Marital status					*0.64*
Not married	25 (17.0)	22 (15.0)	32 (21.9)	79 (18.0)	
Married	103 (70.1)	106 (72.1)	96 (65.8)	305 (69.3)	
Widowed, divorced or separated	19 (12.9)	19 (12.9)	18 (12.3)	56 (12.7)	
Employment (Yes)	120 (81.6)	123 (83.7)	114 (78.1)	357 (81.1)	*0.46*
Alcohol dependence (Yes)	32 (21.8)	29 (19.7)	32 (21.9)	93 (21.1)	*0.88*
Duration of ART treatment[2] (years) (Mean (SD))	5.8 (3.2)	5.3 (3.2)	5.5 (3.1)	5.5 (3.2)	*0.26*
Depression symptoms (PHQ-9≥5) (Yes)	42 (28.6)	36 (24.5)	34 (23.3)	112 (25.5)	*0.55*
Anxiety symptoms (GAD-7≥5) (Yes)	22 (15.0)	24 (16.3)	25 (17.1)	71 (16.1)	*0.88*

([1])For continuous variables, p-values are from one-way ANOVA test; for categorical variables, p-values are from the Wald X2 test.

([2])For this variable, three participants had missing data

Note: SD: standard deviation; PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder-7

6.3.1. Changes in depression and anxiety symptoms over time

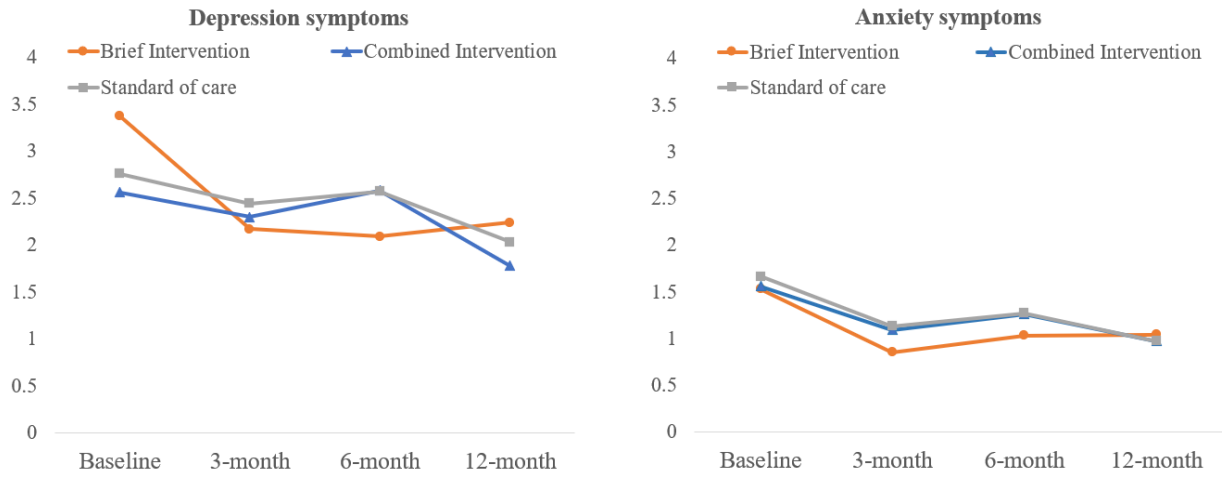


Figure 6.2. Changes in depression and anxiety symptoms from baseline, by intervention arms

There were universal decreases in the proportion of participants having at least mild depression and anxiety symptoms at follow-up. The proportion of participants with depression symptoms at 3-month, 6-month and 12-month visits was 19.0%, 20.5% and 17.6%, respectively. The proportion of participants with anxiety symptoms at 3-month, 6-month and 12-month visits was 7.9%, 10.5% and 7.9%, respectively.

Figure 6.2 shows the means and SD of the continuous depression and anxiety scores over time. Reductions in depression and anxiety symptoms from baseline were observed across all three arms at all follow-up time points, except for depression symptoms in the combined intervention arm at 6 months. At the last follow-up visit, the mean depression scores in the brief and combined intervention arms decreased by 1.14 points (95%CI: -1.87-(-0.40); p=0.003) and 0.78 points (95%CI: -1.34-(-0.23); p=0.006), while the mean depression scores in the SOC decreased by 0.74 points (95%CI: -1.45-(-0.03); p=0.04). These estimates corresponded to a

34%, 30% and 26% change in depression symptoms scores from baseline, respectively. The mean anxiety scores in the brief and combined intervention arms decreased by 0.49 points (95%CI: -0.99-0.01; p=0.05) and 0.59 points (95%CI: -1.12-(-0.05); p=0.03), whereas in the SOC the mean anxiety score decreased by 0.68 points (95%CI: -1.20-(-0.17); p=0.009). These estimates corresponded to a 32%, 38% and 42% change in anxiety symptoms scores from baseline, respectively. All the changes in depression and anxiety symptoms from baseline to 12 months were significantly different than 0 with p-values<0.05, except for anxiety symptoms among the brief intervention group (Table 6.2).

6.3.2. Intervention effects on depression and anxiety symptoms over time, compared to the SOC group

Table 6.2. Changes in depression and anxiety symptoms from baseline, by intervention arms

	3 months	95%CI	p-value	6 months	95%CI	p-value	12 months	95%CI	p-value
Depression symptoms									
Brief Intervention	-1.20	-1.95; -0.46**	0.002	-1.29	-2.04;-0.54***	<0.001	-1.14	-1.87; -0.40**	0.003
Combined Intervention	-0.25	-0.90; 0.39	0.44	0.02	-0.62; 0.67	0.95	-0.78	-1.34; -0.23**	0.006
Standard of care	-0.33	-0.99; 0.33	0.32	-0.20	-0.82; 0.42	0.52	-0.74	-1.45; -0.03*	0.04
Anxiety symptoms									
Brief Intervention	-0.68	-1.20; -0.17*	0.01	-0.50	-1.05; 0.06	0.08	-0.49	-0.99; 0.01	0.05
Combined Intervention	-0.47	-0.86; -0.08*	0.02	-0.29	-0.75; 0.16	0.21	-0.59	-1.12; -0.05*	0.03
Standard of care	-0.52	-0.98; -0.08*	0.02	-0.39	-0.85; 0.06	0.09	-0.68	-1.20; -0.17**	0.009

Note: p-values from One Sample t-test comparing the changes to 0: p<0.05; p<0.01**; p<0.001***; CI: confidence intervals*

Table 6.3. Intervention effects on depression and anxiety symptoms, by follow-up visits*

	3-month			6-month			12-month		
	β	*95%CI*	*p-value*	*β*	*95%CI*	*p-value*	*β*	*95%CI*	*p-value*
Depression symptoms									
BI vs SOC	-0.45	-1.21; 0.31	0.26	-0.67	-1.35; 0.01	0.07	0.02	-0.66; 0.70	0.72
CoI vs SOC	-0.04	-0.82; 0.75	0.81	0.11	-0.65; 0.87	0.78	-0.16	-0.80; 0.48	0.64
BI vs CoI	-0.42	-1.16; 0.32	0.29	-0.78	-1.52; -0.03	0.05	0.18	-0.46; 0.82	0.57
Anxiety symptoms									
BI vs SOC	-0.26	-0.70; 0.18	0.27	-0.14	-0.56; 0.28	0.53	0.09	-0.42; 0.59	0.69
CoI vs SOC	0.01	-0.45; 0.47	0.84	0.05	-0.45; 0.55	0.83	0.05	-0.51; 0.60	0.70
BI vs CoI	-0.27	-0.71; 0.17	0.25	-0.26	-0.77; 0.25	0.34	0.04	-0.47; 0.56	0.77

(*)Models controlled for baseline scores of depression or anxiety symptoms, age, gender, education and employment; β=Mean difference, which indicates the difference between the means of depression/anxiety symptoms of two groups being compared, with the latter group being the reference.
Note: SOC: standard of care; CoI: combined intervention; BI: brief intervention; CoI: confidence interval

After controlling for baseline scores and other covariates, there were no significant associations between receiving either intervention (brief or combined), relative to the SOC, with depression or anxiety symptoms at all follow-up time points (Table 6.3). However, when the two intervention arms were contrasted with each other, being in the brief intervention was associated with marginally significantly fewer depression symptoms at 6 months (Mean difference=-0.78; 95%CI: -1.52-(-0.03); p=0.05). There were no other significant differences in depression and anxiety symptoms between the two interventions at other times.

6.4. Discussion

This study, nested within a randomized trial in rural Vietnam, was among the first to evaluate the impacts of two alcohol interventions on depression and anxiety symptoms among PWH. Depression and anxiety symptoms were common among this sample, with 25.5% and 16.1% of participants reporting mild to severe depression and anxiety symptoms at baseline, respectively. Depression and anxiety symptoms decreased over time across all three arms, and there were no significant impacts of the interventions on these symptoms at follow-up visits.

A systematic review of different alcohol reduction interventions in the general population showed overall improvements in various mental health indicators, such as psychosocial stress levels, self-confidence, contentment with one's life situation and prevalence of psychiatric episodes among participants receiving the interventions being studied[122]. Depression and anxiety symptoms specifically have been examined by only one study, which reported improved depression and anxiety symptoms among in-patients admitted for alcohol use disorders after receiving a detoxification program[123]. However, in that study, improvements in depression were only seen among participants with a significant reduction in drinking, and no comparison group was included to evaluate the relative impacts of the intervention.

Our interventions did not include specific counseling contents on common mental disorders, and the impacts on depression and anxiety symptoms of participants might not be large enough for a significant difference with the SOC group to be observed. Participating in the study, completing assessments over time and receiving SOC services might increase perceived social support and improve the mental health of participants to some extent. Moreover, previous studies also reported a Hawthorne effect, which refers to the change in behaviors due to awareness of being observed in a study[273,274]. Participating in multiple rounds of questionnaire

and having their mental health symptoms evaluated might have led to changes in depression and anxiety symptoms of participants in all three arms. This might help to explain the lack of differential impacts of the intervention groups on these mental health outcomes.

Given the high prevalence of depression and anxiety symptoms in this study and the common co-occurrence of hazardous drinking and common mental health disorders such as depression and anxiety among PWH in the literature[22-24], common mental health disorders should be an important target of change of behavioral interventions for this population. Future studies should seek to design and test alcohol interventions with more intensive mental health care components such as mental health screening and psychosocial counseling for PWH with hazardous alcohol use. These interventions should include participants who are not on ART, since this subgroup might have worse mental health status, compared to those already receiving treatment[288]. In addition, the pathway from these alcohol reductions to mental health symptoms through alcohol use should be further explored to gain a better understanding of how reduced alcohol use might or might not lead to improved mental health.

This study is not without limitations. First, we only recruited ART clients to the trial, and the majority of the participants were male and had a history of injection drug use. People who inject drugs in Vietnam still have the highest prevalence of HIV infection when compared to other key populations such as men who have sex with men and sex workers, despite the fact that the HIV epidemic among this group seems to be declining[289]. Although other samples of PWH in Vietnam also had the majority of participants being male, the proportion of men in this study was higher than that in those studies[290-292]. This might limit my ability to generalize findings to other groups of PWH, including PWH not on ART. Second, since the measures of depression and anxiety symptoms were self-reported, they might be subject to some measurement errors, such as

recall biases. The knowledge of the intervention allocation might have influenced participants' perceived improvements in symptoms if there were differential expectations across intervention groups.

6.5. Conclusions

The prevalence of mild to severe depression and anxiety symptoms was high among this sample of PWH with hazardous alcohol use. A reduction in symptoms was observed among participants receiving two alcohol reduction interventions and the SOC over time but there were no differences in either intervention arm relative to the SOC. Alcohol interventions with a dual focus on alcohol reduction and mental health care are needed to achieve more pronounced and sustainable improvements in depression and anxiety symptoms for PWH with hazardous alcohol use.

CHAPTER 7. ALCOHOL USE AS A MEDIATOR OF THE EFFECT OF TWO ALCOHOL REDUCTION INTERVENTIONS ON MENTAL HEALTH SYMPTOMS OF ART CLIENTS IN VIETNAM

7.1. Introduction

Hazardous drinking, defined as the quantity or pattern of alcohol consumption that increases adverse health outcomes for an individual, is common among people living with HIV (PWH) [15]. Between a quarter to almost half of PWH are hazardous drinkers[14,90,91]. Hazardous alcohol use can have multiple potential harmful effects on PWH. Hazardous alcohol consumption is not only linked to sexual behaviors that increase transmission risks [93] but can also negatively affect HIV treatment by reducing adherence and increasing the risk of treatment failure[16,97-100]. Studies have shown that hazardous drinking is associated with higher odds of detectable viral load among PWH receiving HIV care[103-106]. Motivational Enhancement Therapy (MET) and Cognitive Behavioral Therapy (CBT) are among the most common psychological intervention approaches for reducing alcohol use among those with hazardous alcohol use[28-30]. MET is based on Motivational Interviewing (MI) - a directive, client-centered counseling style that facilitates behavior change by exploring and resolving ambivalence eliciting clients' own motivation for change[119]. MET was first applied in the COMBINE trial, where personalized feedback about alcohol use to the client was added to the intervention to create discrepancy and increase motivation to change[293,294]. CBT consists of a group of psychological therapies that aim to solve negative emotions and dysfunctional behaviors by acknowledging the effects of the environment, cognitions, language and human learning on behaviors[120]. Alcohol reduction interventions based on MET/MI and CBT have been shown to reduce drinking, increase condom

use and improve antiretroviral therapy (ART) adherence among PWH in various settings[28,30,121,251].

Hazardous alcohol use among PWH often co-occurs with common mental health disorders, such as depression and anxiety[21-24,105]. Indeed, PWH who are hazardous drinkers are more than two times as likely to have clinical depression, compared to those who are non-hazardous drinkers[108]. A study among PWH in the US reported that 10.6% had both depression symptoms and harmful levels of alcohol use [22]. Hazardous drinking is strongly related to increased risk of depression and anxiety among PWH. This increased risk is not only due to cognitive and biochemical changes associated with alcohol intake and withdrawal that lead to depressive and anxiety symptoms but also due to other social consequences of hazardous drinking, such as job loss or relationship issues[18-21,107]. Longitudinal studies have shown that reduced alcohol use is associated with significant improvements in mental health outcomes, including depression symptoms[123,295].

Alcohol reduction interventions might impact depression and anxiety directly through the improvements of coping skills, motivation to change and self-confidence, or indirectly through the reduction of alcohol use. Understanding not only if alcohol interventions reduce mental health disorders, but whether they operate indirectly through a reduction in alcohol, or directly to reduce mental health disorders would provide insight into potential resource-efficient approaches to target these comorbidities for PWH. Specifically, alcohol interventions that simultaneously improve the mental health of participants can potentially be a cost-effective and convenient management approach for PWH with co-occurring hazardous alcohol use and mental health disorders.

From March 2016 to May 2018 two different alcohol reduction interventions drawing on MET and CBT were implemented among ART clients with hazardous alcohol use in Vietnam. Both interventions resulted in significant improvement of the primary outcome – percentage of days abstinent from alcohol, compared to a standard of care group, at 12 months after enrollment [251]. Using structural equation modeling to analyze longitudinal data from the main trial, I aimed to examine the mediating role of alcohol use in the pathway from the interventions to depression and anxiety symptoms at the last follow-up visit of participants. Since the interventions had been shown to have positive impacts on alcohol use, I hypothesized that reduced alcohol use would in turn lead to reduced depression and anxiety symptoms at 12 months, and that alcohol use would be a significant mediator in this pathway.

7.2. Methods

7.2.1. Study design and setting

This is a secondary data analysis of the parent study *Reducing Hazardous Alcohol Use & HIV Viral Load: A Randomized Controlled Trial (RCT) in Antiretroviral Treatment (ART) Clinics in Vietnam (REDART)* - a three-arm RCT among hazardous and heavy drinking HIV-positive ART clinic patients in Thai Nguyen, Vietnam. Two alcohol reduction interventions (combined intervention and brief intervention), which both drew from CBT and MET, were compared against each other and compared with the standard of care arm.

ART clients with hazardous alcohol use from 7 ART outpatient clinics in Thai Nguyen - a mountainous, multi-ethnic province located in Northeast Vietnam - were enrolled into the study. Eligibility criteria included those 18 years of age or older; being a current client on ART at one of the study clinics; having hazardous alcohol use (defined as an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score ≥ 4 for men and ≥ 3 for women) and planning to

reside in Thai Nguyen for the next 24 months. Participants who were unable to provide informed consent due to cognitive impairment or having threatening behavior; unwilling to provide locator information or informed consent; and currently participating in another HIV, drug use or alcohol program, study, or intervention were excluded from the study.

7.2.2. Interventions

The combined intervention (CoI) included content from both MET and CBT[193]. It used a client-centered, motivational interviewing approach and focused on developing positive thoughts and skill-building for alcohol use behavior change, including drinking refusal skills and skills to cope with and manage cravings and triggers[32,119]. CoI comprised a total of 6 individual face-to-face sessions and 3 optional group sessions for each participant assigned to this arm, with individual sessions occurring approximately 1 week apart. During these sessions, counselors also reviewed drinking patterns and harmful effects of drinking with patients. There were three optional group sessions that participants assigned to the CoI could choose to attend any time after they enrolled into the study.

The brief intervention (BI) also combined elements from both CBT and MET, but condensed them into a 2-session format [193]. This intervention comprised 2 individual face-to-face sessions and 2 individual booster phone sessions for each participant. The face-to-face sessions occurred approximately 1 month apart, and a phone session occurred 2-3 weeks after each face-to-face session. BI sessions also included a review of drinking patterns, harmful effects of drinking, and alcohol use behavior change strategies.

Participants randomized to the standard of care arm received referrals to alcohol treatment and infectious diseases treatment, as recommended by the Ministry of Health in Vietnam.

7.2.3. Measurements

Alcohol use was measured as percentage of days abstinent from alcohol in the last 30 days, using the timeline follow-back (TLFB) questionnaire at baseline, 3, 6 and 12-month follow-up visits (percentage of days abstinent from alcohol was also the primary alcohol use outcome in the parent study). The TLFB questionnaire has demonstrated high levels of validity and reliability when being used to measure alcohol consumption across different cultures[206,207]. Percentage of days abstinent from alcohol out of the last 30 days was calculated for each visit.

Depression symptoms were assessed at baseline, 3-month, 6-month and 12-month follow-up using the Patient Health Questionnaire-9 (PHQ-9) – a commonly used scale for depression screening[149,194-196]. In Vietnam, the PHQ-9 scale has shown good convergent validity, construct validity and reliability[257], and has been used for a range of populations, including PWH[149,195,196]. The scale evaluates how often the respondent has experienced depression symptoms in the last 2 weeks, such as *"Little interest or pleasure in doing things"* or *"Feeling down, depressed or hopeless".* The total score ranges from 0 to 27[194].

Anxiety symptoms were evaluated with the Generalized Anxiety Disorder-7 (GAD-7) scale at baseline and all follow-up visits. The GAD-7 scale has been validated among PWH and has been used in various Vietnamese populations to measure anxiety[197-200]. Frequency of anxiety symptoms such as "*feeling nervous, anxious, or on edge*", "*not being able to stop or control worrying*" or having "*trouble relaxing*" in the last 2 weeks were assessed, with the total score ranging from 0 to 21[203].

Standard demographics including age, education, income, gender, marital status and employment were collected at baseline. Participants were also asked if they had used any types

of non-injection drugs (including heroin, methamphetamines, etc.) in the last 3 months and if they had ever injected any types of drugs in the past.

7.2.4. Statistical analyses

Longitudinal structural equations models (SEM) were used for the analysis of the mediating role of alcohol use in the association between the intervention and depression/anxiety symptoms, since this technique allows for the assessment of different prospective pathways from the exposure variable to the mediator to the outcomes[224].

Two separate models were run for each of the main outcomes, depression and anxiety symptoms. Coefficients of each of the following pathways were estimated: from the interventions to alcohol use, measured as percentage of days abstinent from alcohol in the last 30 days (a paths); from percentage of days abstinent from alcohol in the last 30 days to depression and anxiety symptoms (b paths) and from the interventions to depression and anxiety symptoms (c' paths). I followed the recommendations of Goldsmith et al. for analyzing the mediation of treatment effects using SEMs[225]. Even though lagged models can better ensure the chronological order between the mediator and outcome, models with contemporaneous paths may be more appropriate in some cases[225]. For example, if the time between the end of the intervention and the first assessment post-intervention is long enough for both the mediator and outcome to change, the potential effects of the mediator on the outcome could have already been observed at this assessment. Therefore, I estimated two different model specifications, one with lagged b-paths (alcohol use at one time point predicting mental health symptoms at the next time point), and one with contemporaneous b paths (alcohol use predicting mental health symptoms at the same time point) (Figure 7.1). The indirect effect via alcohol use was estimated as the product of a paths and b paths for the outcomes. In this study, indirect pathways from the interventions to the

outcomes of depression and anxiety symptoms at 12 months (via alcohol use) included all pathways that went through at least one measure of alcohol use. All other pathways from the interventions to depression and anxiety symptoms at 12 months that only went through previous measures of depression and anxiety symptoms and did not go through any alcohol use measures were considered direct pathways. The total indirect effects and direct effects were calculated for the outcomes at 12 months by summing all corresponding effects at 12 months. Standard errors and 95% confidence intervals (CI) of indirect effects were calculated using the bootstrap procedure (n=5,000)[226]. At 12 months, the total indirect effect via alcohol use was considered significant (i.e., mediation by alcohol use was present) if the 95%CI of the total indirect effect did not include 0. The overall direct, indirect and total effects of the interventions on the outcomes at 3 months and 6 months were presented in the Appendix B (Tables B1, B2 and B3).

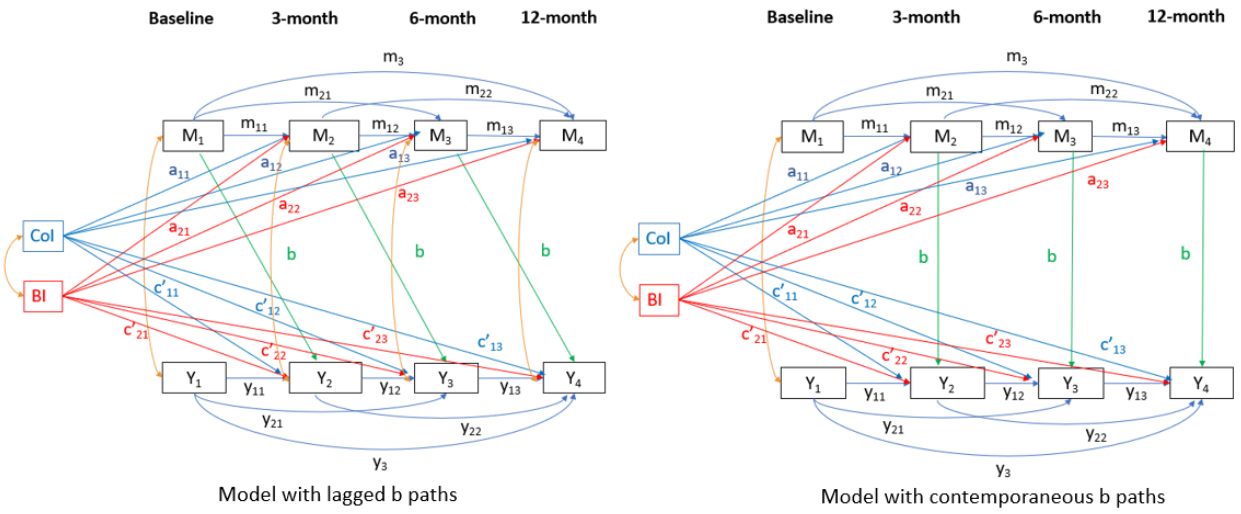


Figure 7.1. Model with lagged and contemporaneous b paths

Note: CoI: Combined Intervention; BI: Brief Intervention; M: Mediator (alcohol use); Y: Outcome (depression or anxiety symptoms)

I first started with basic models having first-level autoregression paths (AR(1)) (measures of alcohol use and mental health symptoms were regressed on immediately preceding measures

only) and no equality constraints (which meant the unstandardized estimates for two parameters of two different paths were not set to be equal). Level-two and level-three autoregression paths (AR(2) and AR(3), i.e., measures of alcohol use and mental health symptoms were regressed on previous two and three values) were then added if they led to significant improvement in model fit. Finally, to make the models more parsimonious, equality constraints of autoregression and b paths were tested and retained if models did not fit significantly worse. Based on the literature, age, gender, non-injection and injection drug use at baseline were chosen a priori and examined as potential confounders[227-233]. Finally, gender was added as a covariate in all models, since it was the only variable significantly correlated with both the mediators and outcomes at $p<0.05$. To further control for unmeasured confounders, AR pathways between measurements of the mediators and outcomes at different time points were included in all models. Moreover, alcohol use and depression/anxiety symptoms assessed at the same time point were allowed to covary, if a contemporaneous path did not already exist between them at that time point[225].

Comparative Fit Index (CFI) and Tucker–Lewis index (TLI) of 0.95 or greater and Root Mean Square Error of Approximation (RMSEA) of less than 0.06 were indicators of good model fit[234]. Even though I reported the chi-square index, it was not used as a fit criterion due to its tendency to reject models with large sample size[235]. Models with a smaller Bayesian Information Criterion (BIC) and Akaike's Information Criterion (AIC) were preferred, and a difference in BIC and AIC of 2 or more points was indicative of significant better fit[225,236]. To compare nested models and test equality constraint assumptions, the Likelihood ratio test and corresponding p-values were used[237]. All reported path coefficients, total overall effect, direct effect and indirect effect coefficients were unstandardized.

Descriptive and correlational statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina). All SEM models were fitted with Mplus 8 (Muthén & Muthén, 2017) using full information maximum likelihood (FIML). FIML also handled missing data, assuming data was missing at random, as recommended by Enders et al[238]. The UNC IRB and the local IRB at the Thai Nguyen Center for Preventive Medicine provided ethics review and approval for the study.

7.3. Results

7.3.1. Sample characteristics

Four hundred and forty participants were enrolled in the study. The mean age of participants at baseline was 39.6 (standard deviation (SD)=5.8). The majority of participants were male (96.8%), married (69.3%), and employed either full-time or part-time (81.1%). The mean depression score of participants at baseline was 2.9 (SD=3.7), and the mean anxiety score was 1.6 (SD=2.9). Participants' characteristics by intervention are presented in Table 7.1. No significant differences in these characteristics across arms were observed.

At the 3-month, 6-month, and 12-month follow-ups, 35 (8%), 30 (7%), and 50 (11%) participants had a missed visit and had missing data on alcohol use and mental health symptoms, respectively.

Table 7.1. Participants' baseline characteristics, by intervention arms

Characteristics N (%)	**Brief intervention (N=147)**	**Combined intervention (N=147)**	**Standard of care (N=146)**	**Total (N=440)**	***p-value****
Age (years) (Mean (SD))	39.8 (5.6)	40.5 (5.8)	40.3 (5.9)	40.2 (5.8)	*0.63*
Male	140 (95.2)	145 (98.6)	141 (96.6)	426 (96.8)	*0.25*
Education					*0.30*
Primary school or less	26 (17.7)	23 (15.7)	17 (11.6)	66 (15.0)	
Some secondary school	74 (50.3)	83 (56.5)	89 (61.0)	246 (55.9)	
Some high school	30 (20.4)	32 (21.8)	24 (16.4)	86 (19.6)	
Some technical training, college or university	17 (11.6)	9 (12.9)	16 (11.0)	42 (9.6)	
Marital status					*0.64*
Not married	25 (17.0)	22 (15.0)	32 (21.9)	79 (18.0)	
Married	103 (70.1)	106 (72.1)	96 (65.8)	305 (69.3)	
Widowed, divorced or separated	19 (12.9)	19 (12.9)	18 (12.3)	56 (12.7)	
Employment (Yes)	120 (81.6)	123 (83.7)	114 (78.1)	357 (81.1)	*0.46*
History of injection drug use (Yes)	122 (83.0)	120 (81.6)	114 (78.1)	356 (80.9)	*0.55*
Number of drinking days in the last 30 days (Mean (SD))	17.6 (10.0)	18.9 (10.2)	17.7 (9.9)	18.1 (10.0)	*0.50*
Number of drinks per drinking day (Mean (SD))	4.0 (3.3)	4.1 (2.9)	4.0 (3.1)	4.0 (3.1)	*0.92*
Depression symptoms (Mean (SD))	3.4 (4.3)	2.6 (3.1)	2.8 (3.6)	2.9 (3.7)	*0.55*
Anxiety symptoms (Mean (SD))	1.5 (2.9)	1.6 (2.8)	1.7 (2.9)	1.6 (2.9)	*0.88*

(*)For continuous variables, p-values are from one-way ANOVA test; for categorical variables, p-values are from the Wald X2 test.

Note: SD: standard deviation; PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder-7

7.3.2. Final model specifications and model fit statistics

Table 7.2. Final model fit statistics

	Depression symptoms		Anxiety symptoms	
b paths	**Lagged**	**Contemporaneous**	**Lagged**	**Contemporaneous**
Chi-square	38.75	45.2	36.81	41.25
Degrees of freedom	20	23	24	28
p-value	0.007	0.004	0.05	0.05
RMSEA	0.046	0.047	0.035	0.033
CFI	0.98	0.98	0.99	0.99
TLI	0.96	0.96	0.98	0.98
BIC	9296	9284	8163	8143
BIC Difference		12		20
AIC	9100	9100	7983	7980
AIC Difference		0		3

Note: RMSEA: Root Mean Square Error of Approximation; CFI: Comparative Fit Index; TLI: Tucker–Lewis index; BIC: Bayesian information criterion; AIC: Akaike's Information Criteria

Table 7.2 shows model fit statistics for models looking at depression and anxiety symptoms as the main outcomes. Even though models with lagged and contemporaneous b paths had similar RMSEA, CFI and TLI, the models with contemporaneous b paths had better fit than those with lagged b paths based on the comparison of BIC and AIC fit indices. For depression symptoms, the AIC indices were equal, but the BIC index of the contemporaneous model was smaller by 12 points. Therefore, models with contemporaneous b paths were therefore chosen as the final models for both mental health symptoms. Estimates of the paths and effects of the alternative lagged models are reported in the Appendix B (Figure B1, Figure B2 and Table B4).

7.3.3. Effects of the interventions on alcohol use (a paths) and effects of alcohol use on mental health symptoms (b paths)

When compared to the SOC, both interventions significantly increased the percentage of days abstinent from alcohol use only at the first follow-up visit (CoI: Mean difference (MD)=0.17, $p<0.001$; BI: MD=0.22, $p<0.001$) (Figures 7.2 and 7.3).

Decreased alcohol use at each follow-up visit was significantly associated with a decrease of 0.57 score in depression symptoms at the same visit (MD=-0.57; p=0.02) (Figure 7.2). However, there was no significant impact of alcohol use on anxiety symptoms (MD=-0.24; p=0.14) (Figure 7.3).

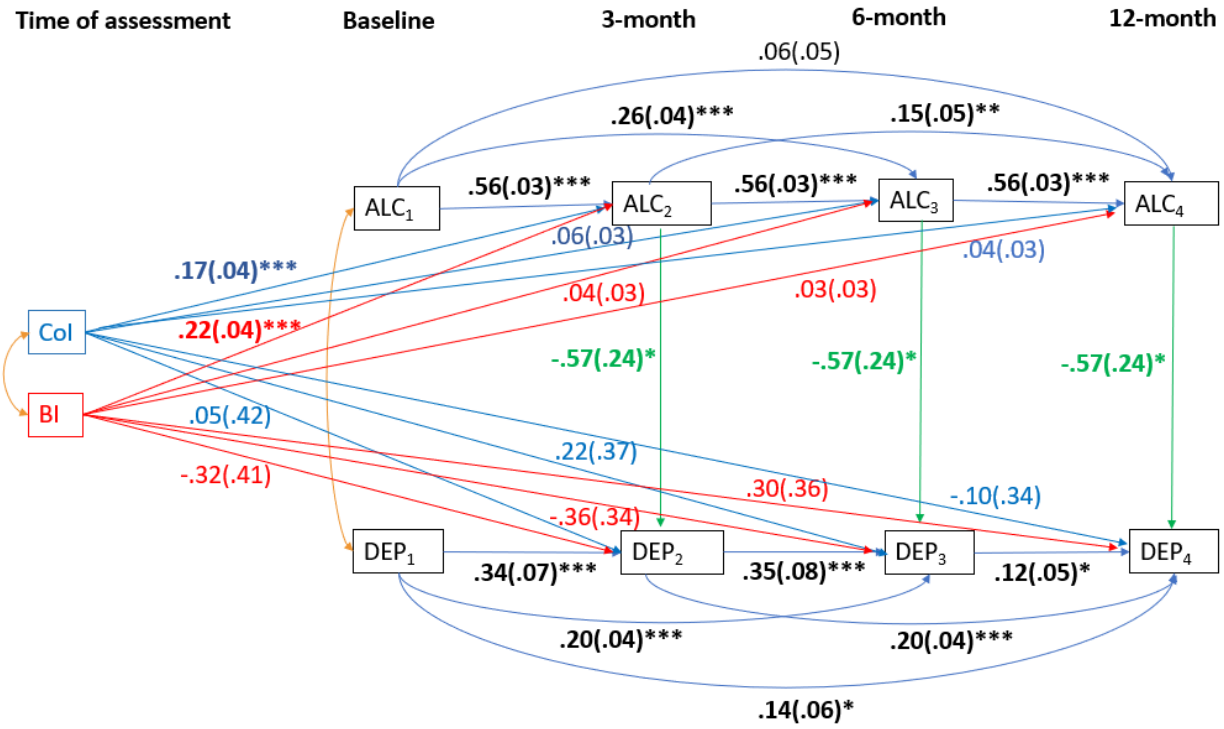


Figure 7.2. Final model examining the mediating role of alcohol use in the effects of two interventions on depression symptoms

Note: CoI: combined intervention; BI: brief intervention; ALC: alcohol use, measured as the percentage of days abstinent from alcohol in the last 30 days; DEP: depression symptoms, measured as the Patient Health Questionnaire-9 score. Gender was regressed on all follow-up measures of alcohol use and anxiety symptoms.
Coefficients (standard errors) of all paths were presented. Significant paths were in bold; (*) p<0.05; (**) p<0.01; (***) p<0.001

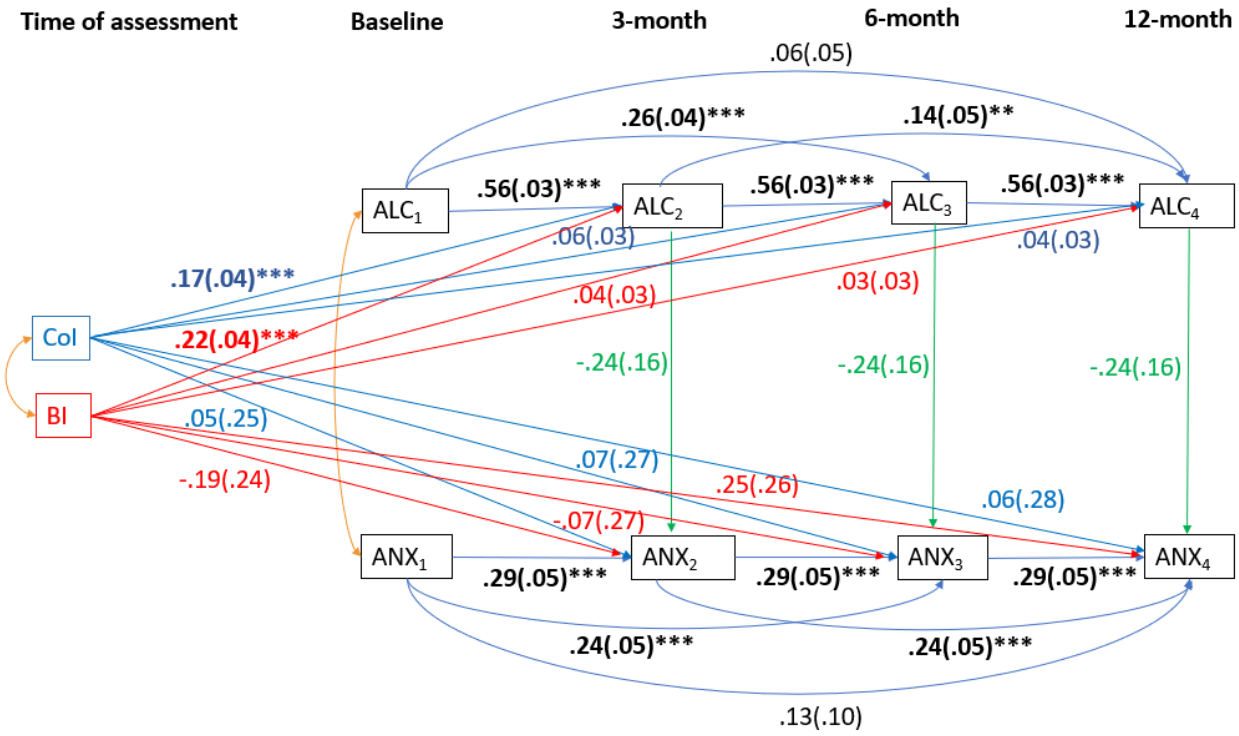


Figure 7.3. Final model examining the mediating role of alcohol use in the effects of two interventions on anxiety symptoms

Note: CoI: combined intervention; BI: brief intervention; ALC: alcohol use, measured as the percentage of days abstinent from alcohol in the last 30 days; ANX: anxiety symptoms, measured as the Generalized Anxiety Disorder-7 score. Gender was regressed on all follow-up measures of alcohol use and anxiety symptoms.

Coefficients (standard errors) of all paths were presented. Significant paths were in bold; (*) p<0.05; (**) p<0.01; (***) p<0.001

7.3.4. Direct and indirect effects of the interventions on mental health symptoms via alcohol use

For each intervention, the overall direct effects of the interventions on mental health symptoms at 12 months were the sum of 4 direct effects through 4 pathways (not going through any measurement of alcohol use). The overall indirect effects of the interventions on mental health symptoms at 12 months were the sum of 8 indirect effects through all 8 pathways (going through at least one measurement of alcohol use). Path specifications and parameters of the final model with contemporaneous b paths were shown in Table 7.3.

Table 7.3. Paths and parameters of direct, indirect and total effects of the interventions on mental health symptoms at 12 months (based on models with contemporaneous b paths)

Effects	Path specifications	Parameters[1], based on intervention	
		CoI	***BI***
Direct effect 1	X->Y_2->Y_3->Y_4	c'11*y12*y13	c'21*y12*y13
Direct effect 2	X->Y_2->Y_4	c'11*y22	c'21*y22
Direct effect 3	X->Y_3->Y_4	c'12*y13	c'21*y13
Direct effect 4	X->Y_4	c'13	c'23
Overall direct effect	**Direct effect 1+2+3+4**		
Indirect effect 1	X->M_2->M_3->M_4->Y_4	a11*m12*m13*b	a21*m12*m13*b
Indirect effect 2	X->M_2->M_3->Y_3->Y_4	a11*m12*b*y13	a21*m12*b*y13
Indirect effect 3	X->M_2->M_4->Y_4	a11*m22*b	a21*m22*b
Indirect effect 4	X->M_2->Y_2->Y_3->Y_4	a11*b*y12*y13	a21*b*y12*y13
Indirect effect 5	X->M_2->Y_2->Y_4	a11*b*y22	a21*b*y22
Indirect effect 6	X->M_3->M_4->Y_4	a12*m13*b	a22*m13*b
Indirect effect 7	X->M_3->Y_3->Y_4	a12*b*y13	a22*b*y13
Indirect effect 8	X->M_4->Y_4	a13*b	a23*b
Overall indirect effect	**Indirect effect 1+2+3+4+5+6+7+8**		
Total effect	**Overall direct effect + overall indirect effect**		

[1]Path parameters correspond to paths specified in the model with contemporaneous b paths, Figure 7.1
Note: X: the intervention (Combined Intervention or Brief Intervention); M: the mediator (alcohol use); Y: the outcome (depression or anxiety symptoms); CoI: Combined Intervention; BI: Brief Intervention

There were significant overall indirect effects via alcohol use of both interventions on depression symptoms at the 12-month follow-up (CoI: MD=-0.134; 95%CI: -0.251-(-0.035); BI: MD=-0.141; 95%CI: -0.261-(-0.038)) (Table 7.4). All overall indirect effects of the interventions on depression symptoms were also significant at 3 months and 6 months (Tables B2 and B3, Appendix B). However, none of the overall direct effects and total effects of the interventions on depression symptoms at 12 months were statistically significant.

All overall indirect effects, direct effects and total effects of both interventions on anxiety symptoms at 12 months were not statistically significant (Table 7.4).

Table 7.4. Direct effects and indirect effects (via alcohol use) of the interventions on depression and anxiety symptoms at 12 months

	Combined Intervention				*Brief Intervention*			
	β	***95%CI***	***SE***	***p-value***	***β***	***95%CI***	***SE***	***p-value***
Depression symptoms								
Overall direct effect	-0.062	-0.662; 0.505	0.36	0.86	0.184	-0.455; 0.819	0.39	0.64
Overall indirect effect	**-0.134**	**-0.251; -0.035**	**0.07**	**0.04**	**-0.141**	**-0.261; -0.038**	**0.07**	**0.04**
Total effect	-0.196	-0.776; 0.360	0.34	0.57	0.043	-0.578; 0.657	0.38	0.91
Anxiety symptoms								
Overall direct effect	0.095	-0.410; 0.589	0.30	0.75	0.171	-0.282; 0.639	0.28	0.54
Overall indirect effect	-0.066	-0.149; 0.006	0.05	0.16	-0.072	-0.165; 0.007	0.05	0.16
Total effect	0.029	-0.468; 0.524	0.30	0.92	0.099	-0.344; 0.551	0.27	0.72

Note: β = Mean difference, which is the difference in mean Patient Health Questionnaire-9/Generalized Anxiety Disorder-7 score at 12 months, when comparing the intervention groups to the standard of care; Significant estimates and bootstrap CIs were in bold; CI: confidence interval; SE: standard error.

7.4. Discussion

To my knowledge, this study was among the first to examine the mediating role of alcohol use in the effects of alcohol reduction interventions on mental health symptoms of PWH. I found that alcohol use, measured as percentage of days abstinent from alcohol in the last 30 days, was a significant mediator of the effects of the alcohol interventions on depression symptoms of participants. Both CoI and BI interventions significantly reduced alcohol use, which in turn was associated with decreased depression symptoms. However, since there was no impact of alcohol use on anxiety symptoms, alcohol use was not a significant mediator of the pathways from the interventions to anxiety symptoms. The total effects of the interventions on both mental health symptoms were also not significant.

The literature on the secondary impact of alcohol reduction interventions on mental health of participants is scarce, and research examining how alcohol use acts as a mediator in this pathway is even more rare. One study among patients with alcohol dependence in the United Kingdom reported significant improvements in depression and anxiety symptoms at 6-month

follow-up and improvements in anxiety symptoms at 1-year follow-up after implementing a detoxification program[123]. The fact that decreased depression symptoms were only reported among those whose drinking was significantly reduced might be indicative of the role of alcohol use in improving depression. However, there was no comparison group in this study to evaluate the relative impacts of the program on mental health, and no formal mediation analysis through changes in alcohol use was conducted.

In this study, positive impacts of alcohol use on depression symptoms were observed. Previous studies in the literature have showed significant associations between high levels of alcohol use and depression, both in the general population and among PWH. For example, one study among drinkers in the US reported that a history of alcohol dependence associated with a 4.2 times increase in the odds of having major depression[20]. A systematic review by Sullivan et al. also found that alcohol problems were strongly correlated with worse depression course, increased suicide/death risk and worse social functioning[296].

I did not find any associations between alcohol use and anxiety symptoms in this study. Research on the relationship between alcohol use and anxiety disorders has been more inconsistent, with some studies reporting a positive association between high levels of alcohol use and more anxiety symptoms (and vice versa)[297-299], while others concluding that alcohol use and alcohol intoxication were actually associated with reduced anxiety[21,300,301]. Among our sample, the mean score of anxiety symptoms was low at baseline (1.5 out of 21). There was little room for anxiety symptoms improvement over time, which might explain the lack of effect of the interventions on anxiety symptoms through alcohol use.

Since alcohol use disorders and mental health problems such as depression and anxiety usually co-exist[21,285,301,302], several treatment approaches have been used for individuals with the

comorbidities of alcohol use disorders and mental disorders, including sequential, parallel and integrated approaches[303]. The sequential approach, which treats one disorder after the other, fails to take into account the reciprocal association between them, while the parallel approach, which includes different providers treating both disorders at the same time, makes it more difficult to coordinate care for patients[304]. Since the integrated approach promotes the simultaneous treatment of both disorders by one single provider, it is preferrable to the other two approaches[303]. In fact, psychological interventions based on MI and CBT are considered ideal to treat these comorbidities, because they can simultaneously target substance use and mental health disorders[285,303,305]. A systematic review on psychological interventions for alcohol misuse among people with co-occurring depression or anxiety disorders found that both MI and CBT-based interventions significantly reduced both depression, anxiety symptoms and alcohol consumption[305]. Brief interventions were also effective in improving mental health symptoms, even though some studies reported better outcomes associated with longer treatment conditions[306,307].

Even though alcohol use was a significant mediator in the pathway from the interventions to depression symptoms, the direct and total effects of interventions on both mental health symptoms were not significant. However, as shown in Table 7.4, the total effect of the CoI on depression symptoms had a larger magnitude than the indirect effect, but was less precise (with a wider 95%CI). Since the 95%CIs of the total effects were wider, they did not reach statistical significance, even when both indirect effects were significant. Compared to the tests of total effect and direct effect, the test of indirect effect can considerably greater power, and requires a much smaller sample size to achieve the same power[308]. Therefore, it is not uncommon to observe a significant mediation even without a total effect to be mediated[308,309]. It is

recommended that researchers continue to test mediation in the absence of total effect, and that the magnitude and significance of the indirect effect should be the focus of the mediation analysis[310,311]. Future studies with larger sample size might have enough power to detect significant effects of these interventions on depression symptoms.

This study has several limitations. First, I was not able to examine the exact mechanism through which reduced alcohol use affects depression and anxiety symptoms. It has been suggested that excessive consumption of alcohol could result in metabolic and nervous system changes that increase the risks for depression and anxiety[285,312]. Moreover, individuals with alcohol misuse are also more likely to experience problems not only in their health but also their work life and social life, which can in turn lead to mental health issues[312]. Qualitative research methods, such as in-depth interviews and focus group discussions, might be necessary to understand how changes in alcohol consumption improve or worsen depression and anxiety symptoms among PWH with hazardous alcohol use. Second, 7-11% of the participants had missing data at different follow-up visits. Missingness at 6-month was associated with both higher depression and anxiety scores at baseline, while missingness at 12-month was associated with only higher depression scores at baseline. I tried to minimize this problem by using the FIML estimator in Mplus, which is a more conservative approach to deal with missing data assuming data were missing at random (MAR)[238]. Finally, the models also made the assumptions of no measurement error of the mediators and outcomes, and no unmeasured confounding between them. When I tried to add measurement error components to the model (i.e., including measured and latent variables of the mediators and outcomes), the model fit became worse, thus I decided to report the models without measurement errors. I also controlled for confounding by different methods, such as allowing for covariances between alcohol use and mental health

symptoms at the same time point, and including autoregression pathways. Finally, by using the PHQ-9 and GAD-7 scales, we could not determine whether participants with mental health symptoms in our study merely had a larger psychiatric diagnosis or only exhibited symptoms without a clinical diagnosis. Interventions targeting participants with substance use disorders may use a diagnostic interview (such as the Mini-International Neuropsychiatric Interview) to better distinguish between mental health symptoms and a mental health disorder diagnosis, because sometimes the improvement in mental health is a mere result of the reduction in substance-induced symptoms[313].

Despite the limitations, this study makes valuable contributions to the understanding of whether and how alcohol use mediates the pathway between alcohol reduction interventions and mental health symptoms, namely depression and anxiety among PWH. Future alcohol interventions should incorporate mental health components to increase the magnitude of the total effects on common mental health problems such as depression and anxiety symptoms. Studies with larger, more representative samples can compare and evaluate the cost-effectiveness of interventions solely focusing on alcohol reduction versus alcohol interventions that integrate components of mental health care.

7.5. Conclusions

Alcohol use, measured as percentage of days abstinent from alcohol in the last 30 days, was a significant mediator of the effects of two alcohol interventions on depression symptoms, but not anxiety symptoms of ART clients in Thai Nguyen, Vietnam. More research, especially interventions that equally highlight mental health and alcohol disorders as well as cost-effectiveness studies focusing on PWH with these comorbidities, are needed to determine and further evaluate the optimal ways to tackle these common comorbidities among PWH.

CHAPTER 8. DISCUSSION AND CONCLUSION

8.1. Summary of aims and findings

8.1.1. Paper 1 (Aim 1 and Sub-aim 1)

The aims of the first paper (Chapter 5) were to (1) evaluate the longitudinal association between depression, anxiety symptoms and two HIV outcomes (viral suppression and complete ART adherence) among ART clients with hazardous alcohol use in the parent trial; and (2) determine whether alcohol dependence modifies the longitudinal association between depression, anxiety symptoms and HIV outcomes. No overall effect of depression and anxiety symptoms on viral suppression was observed throughout the study. However, I found that anxiety symptoms were associated with a small increase in the probability of viral suppression only at the last follow-up. Since an inverted U-shaped association between arousal, anxiety, and performance[275,276] has been reported, I hypothesized that by participating in multiple rounds of interviews, participants with milder anxiety symptoms might become more aware of and worried about their health's status, and therefore more motivated to take action to improve their overall health.

I was also able to demonstrate that an increase in depression or anxiety symptoms was associated with a decreased probability of complete ART adherence, defined as no missed pills in the last three months. This study also supported a modifying effect of alcohol dependence on the association between anxiety symptoms and ART adherence in this group. More specifically, the negative effects of anxiety symptoms on ART adherence were stronger among participants with alcohol dependence, compared to those without. This finding highlighted the importance of

tackling co-existing problems commonly seen among PWH, such as alcohol dependence and mental health disorders, due to their syndemic interaction to worsen HIV outcomes.

8.1.2. Paper 2 (Aim 2)

The aims of the second paper (Chapter 6) were to (1) describe the changes in depression and anxiety symptoms of ART clients who are hazardous drinkers in the parent trial over time and (2) assess the impact of two evidence-based alcohol-reduction interventions on depression and anxiety symptoms at 3, 6, and 12 months post-intervention, comparing the effects of the two interventions to each other and to the SOC group. I found that depression and anxiety symptoms were common among ART clients with hazardous alcohol use at baseline (the proportion of participants having depression and anxiety symptoms at baseline was 25.1% and 16.1%, respectively). A decrease in depression and anxiety symptoms were observed in all three arms from baseline to 12-month follow-up, with largest absolute change observed in the BI arm for depression symptoms and the SOC arm for anxiety symptoms. GEE models were used to evaluate the longitudinal effects of the interventions on depression and anxiety symptoms, controlling for baseline scores and other covaries. However, I did not see no significant differences in depression and anxiety symptoms among participants receiving either intervention, relative to the SOC.

8.1.3. Paper 3 (Aim 3)

In the third paper (Chapter 7), using structural equation modeling to analyze longitudinal data from the main trial, I aimed to examine the mediating role of alcohol use in the pathway from the interventions to depression and anxiety symptoms at the last follow-up visit of participants. Since the interventions had been shown to have positive impacts on alcohol use, I hypothesized that reduced alcohol use would in turn lead to reduced depression and anxiety

symptoms at 12 months, and that alcohol use would be a significant mediator in this pathway. This study was among the first to examine the effects of alcohol reduction interventions on mental health symptoms of PWH via alcohol use. I found that alcohol use, measured as percentage of days abstinent from alcohol in the last 30 days, was a significant mediator of the effects of the alcohol interventions on depression symptoms of participants. Both CoI and BI interventions significantly reduced alcohol use, which in turn was associated with decreased depression symptoms. However, there was no significant impact of alcohol use on anxiety symptoms, therefore alcohol use did not mediate the pathways from the interventions to anxiety symptoms. The total effects of the interventions on both mental health symptoms were also not significant. This was not unexpected, since intervention content primarily focused on alcohol use instead of mental health disorders. However, the findings demonstrated that decreased alcohol use itself could lead to decreased depression symptoms over time, and that changing the level of alcohol use could play an important role in improving depression symptoms for PWH with hazardous drinking.

8.2. Key discussion points

8.2.1. Intervention implications

8.2.1.1. The need for mental health interventions among PWH

The results from this dissertation have implications for future interventions focusing on mental health among PWH. I found high prevalence of depression and anxiety symptoms among this sample of ART clients with hazardous alcohol use in Vietnam. Moreover, these mental health symptoms lead to sub-optimal adherence over time, and anxiety symptoms interacted with alcohol dependence to further reduce ART adherence. These findings highlighted the urgent need for interventions targeting depression and anxiety for the vulnerable group of PWH with

high levels of alcohol use. However, the knowledge and awareness of mental health disorders among PWH remain low[314,315]. For example, the lack of awareness and denial of mental health problems, confirmed by not only PWH but also HIV providers in Vietnam, were found to be a significant barrier to mental health care seeking behaviors[314]. Therefore, the first important step is to raise awareness about the seriousness of mental health problems among PWH, especially those with co-morbidities such as alcohol use disorders. In addition, mental health services such as screening, counseling or medication treatment are essential to improve not only mental health, but also HIV outcomes and the overall well-being for PWH with hazardous alcohol use. Transdiasgnostic interventions, which apply the same underlying treatment principles across mental disorders without tailoring the protocol to specific diagnoses[316], might also be necessary, given that a lot of patients can have multiple mental health disorders at the same time.

In one of the studies, although lower level of alcohol use led to fewer depression symptoms, I was not able to demonstrate a significant total effect of both interventions, CoI and BI, on depression and anxiety symptoms. This might be because the counseling sessions of the alcohol reduction interventions did not include any mental health care components. Given the promising findings on the effects of reduced alcohol use on mental health symptoms, alcohol interventions with a dual focus on alcohol reduction and mental health care should be implemented to achieve more pronounced and sustainable improvements in mental health status for PWH with hazardous alcohol use. In fact, psychological interventions based on MI and CBT are considered a great option to treat these comorbidities, because they can simultaneously target substance use and mental health disorders[285,303,305]. A systematic review on psychological interventions for alcohol misuse among people with co-occurring depression or anxiety disorders found that both MI and CBT-based interventions significantly reduced both depression, anxiety

symptoms and alcohol consumption[305]. Treatment approaches such as sequential, parallel and integrated approaches have been proposed for individuals with the comorbidities of alcohol use disorders and mental disorders[303]. The integrated approach is considered more preferrable to the other two approaches due to its ability to promotes the simultaneous treatment of both disorders by one single provider[303]. However, mental health interventions targeting participants with substance use disorders may use a diagnostic interview (such as the Mini-International Neuropsychiatric Interview) to better distinguish between mental health symptoms and a mental health disorder diagnosis, because sometimes the improvement in mental health is a mere result of the reduction in substance-induced symptoms[313].

Studies have shown that both MI and CBT-based interventions have great potentials to treat individuals in the general population with co-morbidities of alcohol use and mental health disorders, due to their ability to reduce both mental health symptoms and alcohol consumption[285,303,305]. However, in a systematic review on psychological interventions for alcohol misuse among people with co-occurring depression or anxiety disorders, none of the interventions reported was implemented among PWH. Additional studies should be done to test these integrated interventions among the specific group of PWH, who are even more susceptible to these co-morbidities but facing more barriers to access to care[64,143,314,315]. In addition, PWH suffer from unique challenges and stressors associated with HIV infection, including health-related concerns, financial difficulties as well as discrimination, stigma and lack of social support, which can lead to alcohol misuse and mental health issues[44-49]. Therefore, interventions for PWH with co-occurring alcohol use and mental health disorders must take into account these unique challenges to reduce their alcohol intake and improve their mental health.

I found that compared to the CoI, the BI significantly reduced depression symptoms at 6 months, even though the impact was not sustained at 12 months. In the main paper of the trial that has recently been published, the BI was equally effective as, if not better than the CoI in reducing alcohol use and improving viral suppression among participants[251]. Since the BI is shorter, less intensive and needs fewer resources, it can potentially be the better and more cost-effective intervention of the two options to be delivered to PWH who are hazardous drinkers in low-resource settings.

8.2.1.2. The need for implementation research studies

Despite high prevalence of depression, anxiety among PWH and their serious HIV and non-HIV related consequences, globally mental health care for PWH continue to be overlooked, and mental health issues are often under-diagnosed and under-treated among this group[64,242,317]. Studies among PWH in LMIC revealed numerous personal and organization challenges to accessing mental health services, including HIV and mental-health related stigma, lack of awareness around mental health issues, limited human resources, lack information on available mental health services and fragmented health system[314,315,318]. As a result, mental health services and facilities dedicated to the marginalized population of PWH are even more scarce[146,314,315,318].

Therefore, even when an intervention is proved to be effective in a research setting, there might be numerous barriers to implementing such an intervention in a low-resource setting. For example, in Vietnam the average number of psychiatrist and psychologist per 100,000 population was only 0.91 and 0.09, respectively[319]. Psychiatrists in Vietnam only work in mental hospitals or psychiatric departments in general hospitals, leading to a serious lack of mental health care access in outpatient settings[320]. Moreover, even if mental health care exists, concerns about affordability of such services still exist among PWH, which greatly affect their willingness to

receive mental health care[314]. It would be impossible to successfully scale up mental health interventions for PWH without taking into account these real-world challenges and coming up with appropriate implementation strategies to overcome them. Future implementation science research in this area is warranted to ensure feasibility, acceptability and effectiveness of evidence-based interventions targeting PWH with co-occurring alcohol use and mental health disorders in LMIC. Implementation science studies will help us understand the barriers and facilitators of the implementation of mental health interventions in LMIC, as well as identify appropriate implementation strategies to overcome these barriers.

For example, mental health services should be integrated into existing HIV primary care, especially in low- and middle- income countries (LMIC) by using existing human resources in HIV programs. The integration of mental health screening and treatment into HIV care was indeed identified as a crucial step towards achieve the UNAIDS 90-90-90 goals in low-resource settings[321]. Several studies have also tested different models of task-shifting to treat common mental health disorders in low-resource settings, such as in sub-Saharan Africa where there is a paucity of mental health care providers[322-325]. Task-shifting is defined as a rational distribution of tasks among the health workforce teams, where specific tasks are moved from highly qualified health workers to those with shorter training and fewer qualifications[326]. It has been shown to be a feasible and effective strategy to improve mental health symptoms, not only for the general population but also for PWH in sub-Saharan Africa [322,324,325]. However, no intervention using task-shifting as an implementation strategy to provide mental health care for PWH has been done in Vietnam. Further implementation studies testing the feasibility and cost-effectiveness of this model in Vietnam is necessary to scale up mental health care for PWH with comorbidities given limited existing resources.

8.2.2. Implications for future research

8.2.2.1. The interaction of different co-morbidities on ART adherence and viral suppression among PWH

It is important to examine how alcohol use and mental health symptoms interact to affect ART adherence and HIV viral load, given that about 10% of PWH suffer from co-occurring mental health and alcohol use disorders[22]. Study 1 was among the first to examine the syndemic interaction of alcohol use and mental health symptoms among PWH, and I found that the negative effects of anxiety symptoms on ART adherence were stronger among participants with alcohol dependence. However, I was not able to make inference on the broader group of PWH, since only PWH in Vietnam who are on ART and have hazardous alcohol use were recruited. In order to make findings more generalizable, future studies should include other groups of PWH, such as PWH without hazardous alcohol use, PWH who are not on ART and PWH in other countries.

PWH are affected by numerous co-morbidities other than alcohol use and mental health disorders, such as smoking, drug abuse and other sexually transmitted infections[114,171,327]. These comorbidities are often the consequences of HIV infection or associated risk factors and risky behaviors[328,329]. Previous studies have shown that PWH have significantly more comorbidities than their HIV-negative counterparts, and that about 30% of PWH have at least one comorbid condition[116,329,330]. Increased numbers of comorbidities were also associated with higher HIV viral loads and worse ART adherence[114,116,171]. The syndemic approach, which aims to explain why certain diseases and conditions usually co-occur, and to explore the pathways through which they interact to enhance the negative effects of diseases[164], was applied in the first study of this dissertation. It can be expanded in future research to identify the most vulnerable sub-group of PWH with co-morbidities, to determine the mechanisms through which these comorbidities

interact to affect HIV outcomes and to guide combined interventions incorporating different components targeting the comorbidities.

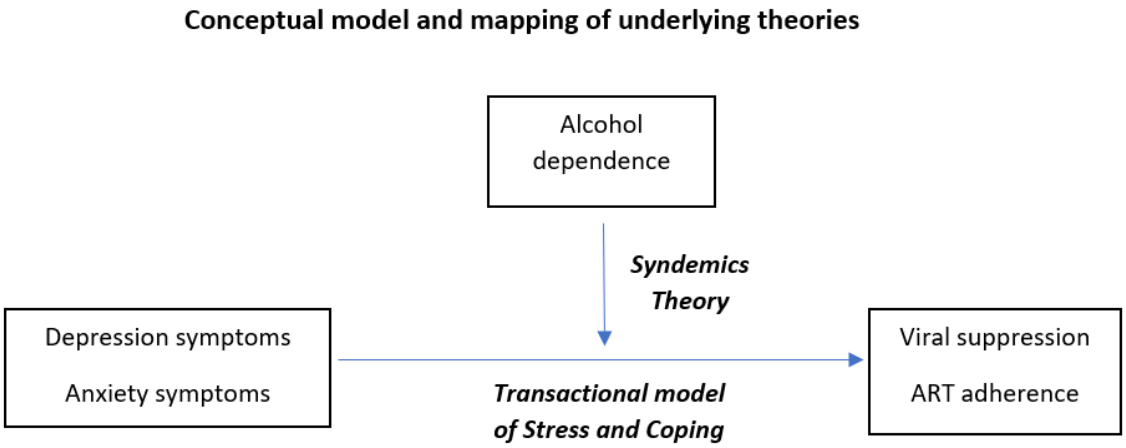
8.2.2.2. Mediation and moderation research on the potential effects of alcohol use on mental health symptoms among PWH

In one of the studies, lower levels of alcohol use were associated with fewer symptoms of depression, but were not associated with anxiety symptoms. Conflicting findings have been reported on the association between alcohol use and common mental health disorders. While some studies found that higher levels of alcohol use correspond to more mental health symptoms[297,298,331], others showed no association, or associations in the opposite direction (higher alcohol use associated with reduced symptoms)[21,146,300,301]. More longitudinal research is needed to explore how alcohol use affects common mental health disorders among PWH, and if a U-shape relationship exists. A study among PWH in Vietnam showed that even though hazardous drinking was associated with higher likelihood of having depression symptoms, social support acted as a buffer in this association, such that it was only significant among those with low levels of social support[331]. Future studies should seek to understand not only the potential mechanisms through which alcohol use affect mental health, but also potential factors that might affect this relationship, such as social support, alcohol norms and stigma. Qualitative research methods, such as in-depth interviews and focus group discussions might be able to shed more light on how different levels of alcohol consumption influences depression and anxiety symptoms among PWH, and whether the effects depend on other interpersonal and environmental factors.

8.2.2.3. Multi-level interventions targeting alcohol use and mental health for PWH where social norms around alcohol use exist

As I have mentioned in the discussion above, the interrelationship between alcohol use and mental health among PWH is complicated because it also depends on different social and environmental factors. PWH have unique challenges that make alcohol abstinence challenging. First, PWH can be particularly susceptible to alcohol abstinence stigma, which is stigma associated with abstaining or reducing alcohol consumption, especially in social contexts[245]. In Vietnam, social drinking and social support are perceived as closely intertwined[143]. In fact, it has been shown in one study that no alcohol use was actually associated with depression symptoms among HIV-positive PWID in Vietnam, and in another study that hazardous drinking was not associated with depression symptoms among PWH who receive social support[148,331]. Second, the social pressure to drink in social events among men in Vietnam might be so high that those who refuse to drink at such events might be perceived as rude, abnormal or having an illness[143]. This might make it even more difficult for PWH who do not want to disclose their HIV status to refuse drinking. Finally, PWH might use alcohol as a coping mechanism for stress, because alcohol use can help improve mood to an extent[143]. Therefore, the efforts to reduce alcohol use and improve mental health symptoms among PWH should not stop at the interpersonal level. It would be challenging to change individual's drinking behaviors and mental health status in a context where very powerful norms around alcohol exist and strongly affect such behaviors. Multi-level interventions that aim to tackle not only individual behaviors, but also political and social contexts around drinking are strongly encouraged because this holistic approach would have a lot more potential to make simultaneous positive impacts on alcohol use and mental health of PWH.

APPENDIX A. SUPPLEMENTARY TABLES AND FIGURES FOR CHAPTER 5



1. **Figure A1. Conceptual model and mapping of underlying theories**

2. Table A1. Associations between depression, anxiety symptoms and HIV outcomes at the next visit (Models with interaction terms)

Table A1. Associations between depression, anxiety symptoms and HIV outcomes at the next visit[1]

	Viral supression[2]			ART adherence[3]		
	aRR	**95%CI**	**p-values**	**aRR**	**95%CI**	**p-values**
Main predictor: Depression symptoms						
Depression symptoms (at the previous timepoint)	1.07	0.77-1.47	0.7	0.90	0.85-0.96	0.002
Time (of outcome assessment)						
3-month	1.00	***	***	1.00	***	***
6-month	1.01	0.95-1.08	0.7	0.93	0.87-0.99	0.04
12-month	0.96	0.90-1.02	0.19	0.96	0.89-1.02	0.19
Interaction terms						
Depression symptoms x 6-month	0.98	0.90-1.06	0.58	1.06	0.97-1.16	0.22
Depression symptoms x 12-month	1.06	0.98-1.15	0.16	1.12	1.03-1.23	0.01
Wald test for joint significance[4]			0.13			0.05
Main predictor: Anxiety symptoms						
Anxiety symptoms (at the previous timepoint)	0.96	0.89-1.04	0.29	0.87	0.80-0.95	0.002
Time (of outcome assessment)						
3-month	1.00	***	***	1.00	***	***
6-month	1.00	0.94-1.06	0.97	0.95	0.89-1.01	0.09
12-month	0.95	0.90-1.01	0.1	0.97	0.91-1.03	0.28
Interaction terms						
Anxiety symptoms x 6-month	1.00	0.89-1.13	0.95	1.03	0.90-1.18	0.63
Anxiety symptoms x 12-month	1.14	1.02-1.27	0.02	1.20	1.06-1.36	0.003
Wald test for joint significance[4]			0.04			0.01

[1]Each multivariable model has only one mental health predictor, either depression symptoms or anxiety symptoms; models with the same outcome have the same set of covariates. aRRs were associated with a 5-point increase in scores of depression or anxiety symptoms at the previous time point

*[2]Models predicting viral suppression controlled for age, viral suppression at baseline, intervention exposure, time, interaction of time*depression/anxiety symptoms*

*[3]Models predicting adherence controlled for marital status, alcohol dependence at baseline, adherence at baseline, intervention exposure, time, interaction of time*depression/anxiety symptoms*

[4]p-value of the Wald test for joint significance of all interaction terms in the model

Note: ART: antiretroviral therapy; aRR: adjusted risk ratio; CI: confidence interval

3. Table A2. Effect modification of baseline viral suppression on the associations between depression, anxiety symptoms and viral suppression

Table A2.1. Effect modification of baseline viral suppression on the associations between depression, anxiety symptoms and viral suppression[1]

	aRR	95%CI	p-values
Main predictor: Depression symptoms			
Depression symptoms	0.99	0.95-1.02	0.42
Depression symptoms x Viral suppression at baseline	0.89	0.79-0.99	0.04
Main predictor: Anxiety symptoms			
Anxiety symptoms	0.98	0.93-1.03	0.44
Anxiety symptoms x Viral suppression at baseline	0.88	0.76-1.01	0.07

*[1]All models controlling for age, viral suppression at baseline, intervention exposure, time, interaction of baseline viral suppression*depression/anxiety symptoms*
Note: aRR: adjusted risk ratio; CI: confidence interval

Table A2.2. Associations between depression symptoms and viral suppression, stratified by baseline viral suppression[1]

	aRR	95%CI	p-values
Viral suppression at baseline	0.99	0.96-1.01	0.32
No viral suppression at baseline	1.11	0.98-1.27	0.14

*[1]All models controlling for age, viral suppression at baseline, intervention exposure, time, interaction of baseline viral suppression*depression/anxiety symptoms*
Note: aRR: adjusted risk ratio; CI: confidence interval

4. Table A3. Missing data of depression, anxiety symptoms and HIV outcomes at follow-up visits

Table A3. Missing data of depression, anxiety symptoms and HIV outcomes at follow-up visits

	3-month		*6-month*		*12-month*	
	N	***%***	***N***	***%***	***N***	***%***
Mental health						
Depression symptoms *Anxiety symptoms*	35	8	30	7	50	11
HIV outcomes						
Complete ART adherence	40	9	39	8	53	12
Viral suppression	37	8	30	7	50	11

Note: ART: antiretroviral therapy

APPENDIX B. SUPPLEMENTARY TABLES AND FIGURES FOR CHAPTER 7

1. **Table B1. Paths and parameters of direct, indirect and total effects of the interventions on mental health symptoms at 3 and 6 months (based on models with contemporaneous b paths)**

Table B1. Paths and parameters of direct, indirect and total effects of the interventions on mental health symptoms at 3 and 6 months (based on models with contemporaneous b paths)

Effects	Path specifications	Parameters[1], based on intervention	
		CoI	***BI***
3-month			
Direct effect 1	X->Y_2	c'11	c'21
Overall direct effect	Direct effect 1	c'11	c'21
Indirect effect 1	X->M_2->Y_2	a11*b	a21*b
Overall indirect effect	Indirect effect 1	a11*b	a21*b
Total effect	Overall direct effect + overall indirect effect		
6-month			
Direct effect 1	X->Y_2->Y_3	c'11*y12	c'21*y12
Direct effect 2	X->Y_3	c'12	c'22
Overall direct effect	Direct effect 1+2		
Indirect effect 1	X->M_2->M_3->Y_3	a11*m12*b	a21*m12*b
Indirect effect 2	X->M_2->Y_2->Y_3	a11*b*y12	a21*b*y12
Indirect effect 3	X->M_3->Y_3	a12*b	a22*b
Overall indirect effect	Indirect effect 1+2+3		
Total effect	Overall direct effect + overall indirect effect		

[1]Path parameters correspond to paths specified in the model with contemporaneous b paths, Figure 7.1

Note: X: the intervention (Combined Intervention or Brief Intervention); M: the mediator (alcohol use); Y: the outcome (depression or anxiety symptoms); CoI: Combined Intervention; BI: Brief Intervention

2. 3. Table B2. Direct effects and indirect effects (via alcohol use) of the interventions on depression symptoms at 3 and 6 months (based on the final model with contemporaneous b paths)

Table B2. Direct effects and indirect effects (via alcohol use) of the interventions on depression symptoms at 3 and 6 months (based on the final model with contemporaneous b paths)

	Combined Intervention				***Brief Intervention***			
Intervention	***β***	***95%CI***	***SE***	***p-value***	***β***	***95%CI***	***SE***	***p-value***
3-month								
Total effect	0.047	-0.652; 0.728	0.42	0.91	-0.319	-1.003; 0.362	0.41	0.44
Indirect effect	**-0.099**	**-0.182; -0.027**	**0.05**	**0.04**	**-0.124**	**-0.224; -0.034**	**0.06**	**0.03**
Direct effect	-0.052	-0.748; 0.626	0.41	0.90	-0.443	-1.123; 0.220	0.41	0.28
6-month								
Total effect	0.236	-0.425; 0.886	0.40	0.55	-0.473	-1.073; 0.128	0.37	0.20
Indirect effect	**-0.123**	**-0.231; -0.032**	**0.06**	**0.05**	**-0.134**	**-0.252; -0.034**	**0.07**	**0.05**
Direct effect	0.113	-0.543; 0.757	0.39	0.78	-0.607	-1.194; -0.020	0.36	0.09

Note: β = Mean difference, which is the difference in mean Patient Health Questionnaire-9 score at each time point, when comparing the intervention groups to the standard of care; Significant estimates and bootstrap CIs were in bold; CI: confidence interval; SE: standard error

4. **Table B3. Direct effects and indirect effects (via alcohol use) of the interventions on anxiety symptoms at 3 and 6 months (based on the final model with contemporaneous b paths)**

Table B3. Direct effects and indirect effects (via alcohol use) of the interventions on anxiety symptoms at 3 and 6 months (based on the final model with contemporaneous b paths)

	Combined Intervention				***Brief Intervention***			
Intervention	***β***	***95%CI***	***SE***	***p-value***	***β***	***95%CI***	***SE***	***p-value***
3-month								
Total effect	0.045	-0.364; 0.439	0.25	0.85	-0.187	-0.585; 0.196	0.24	0.44
Indirect effect	-0.041	-0.093; 0.004	0.03	0.16	-0.053	-0.121; 0.005	0.04	0.16
Direct effect	0.004	-0.401; 0.401	0.25	0.99	-0.240	-0.635; 0.138	0.24	0.31
6-month								
Total effect	0.083	-0.362; 0.514	0.26	0.76	-0.123	0.565; 0.340	0.27	0.65
Indirect effect	-0.049	-0.110; 0.004	0.04	0.16	-0.055	-0.124; 0.005	0.04	0.17
Direct effect	0.034	-0.415; 0.472	0.27	0.90	-0.177	-0.610; 0.276	0.27	0.50

Note: β = Mean difference, which is the difference in mean Generalized Anxiety Disorder-7 score at each time point, when comparing the intervention groups to the standard of care; CI: confidence interval; SE: standard error

5. **Figure B1. Alternative model with lagged b paths examining the mediating role of alcohol use in the effects of two interventions on depression symptoms**

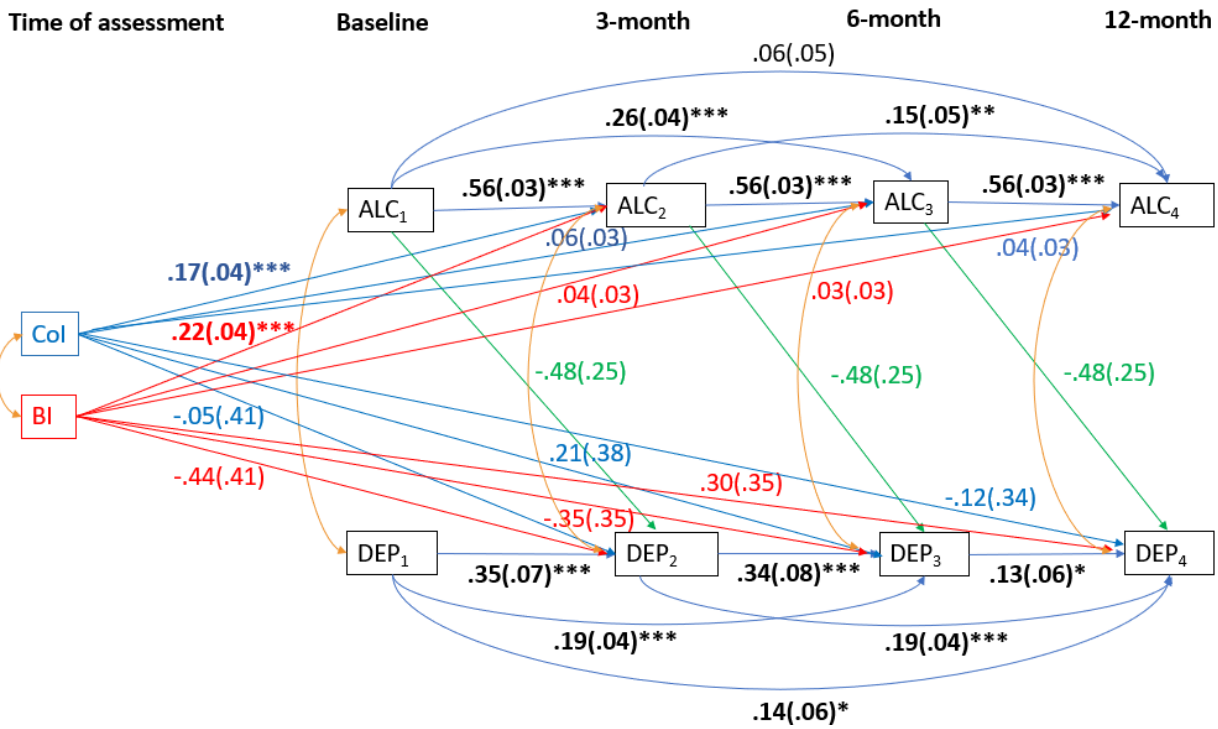


Figure B1. Alternative model with lagged b paths examining the mediating role of alcohol use in the effects of two interventions on depression symptoms

Note: CoI: combined intervention; BI: brief intervention; ALC: alcohol use, measured as the percentage of days abstinent from alcohol in the last 30 days; DEP: depression symptoms, measured as the Patient Health Questionnaire-9 score. Gender was regressed on all follow-up measures of alcohol use and anxiety symptoms.
Coefficients (standard errors) of all paths were presented. Significant paths were in bold; (*) p<0.05; (**) p<0.01; (***) p<0.001

6. **Figure B2. Alternative model with lagged b paths examining the mediating role of alcohol use in the effects of two interventions on anxiety symptoms**

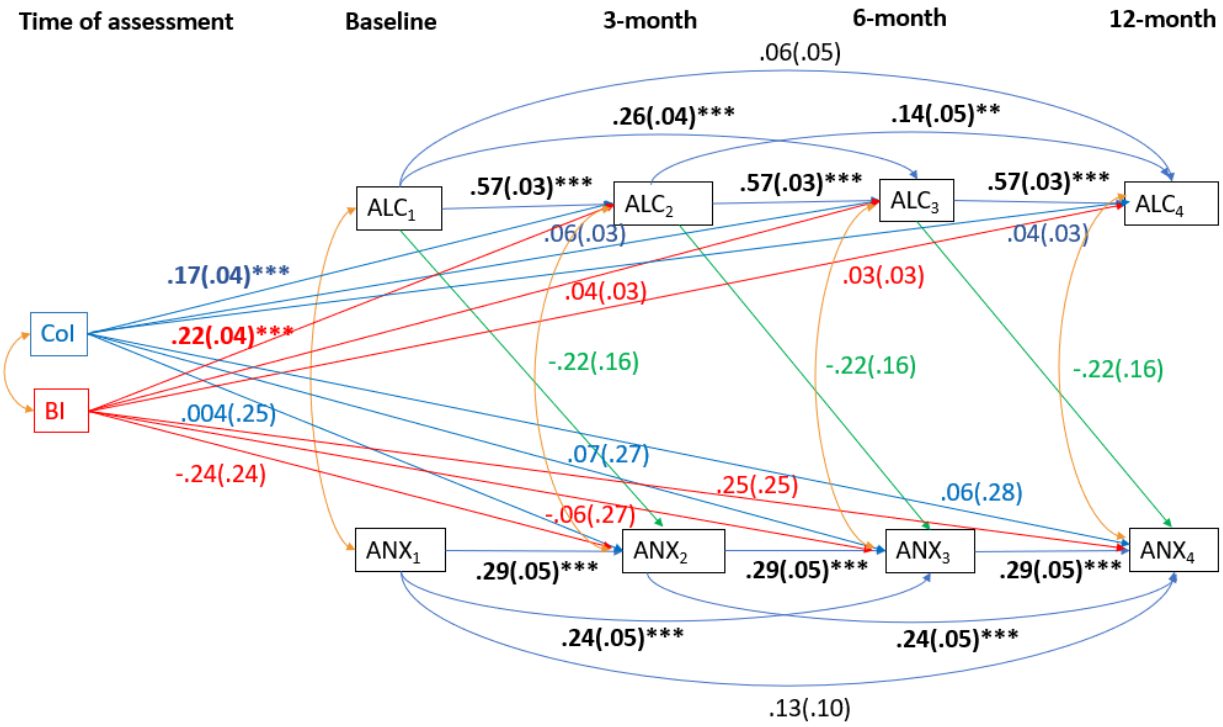


Figure B2. Alternative model with lagged b paths examining the mediating role of alcohol use in the effects of two interventions on anxiety symptoms

Note: CoI: combined intervention; BI: brief intervention; ALC: alcohol use, measured as the percentage of days abstinent from alcohol in the last 30 days; ANX: anxiety symptoms, measured as the Generalized Anxiety Disorder-7 score. Gender was regressed on all follow-up measures of alcohol use and anxiety symptoms.

Coefficients (standard errors) of all paths were presented. Significant paths were in bold; (*) p<0.05; (**) p<0.01; (***) p<0.001

7. **Table B4. Direct effects and indirect effects (via alcohol use) of the interventions on depression and anxiety symptoms at 12 months, based on the alternative model with lagged b paths**

Table B4. Direct effects and indirect effects (via alcohol use) of the interventions on depression and anxiety symptoms at 12 months, based on the alternative model with lagged b paths

	Combined Intervention				***Brief Intervention***			
	β	***95%CI***	***SE***	***p-value***	***β***	***95%CI***	***SE***	***p-value***
Depression symptoms								
Overall direct effect	-0.100	-0.692; 0.463	0.35	0.78	0.149	-0.481; 0.774	0.38	0.70
Overall indirect effect	-0.086	-0.172; -0.008	0.05	0.09	-0.091	-0.185; -0.009	0.06	0.10
Total effect	-0.185	-0.765; 0.373	0.35	0.59	0.058	-0.564; 0.678	0.38	0.88
Anxiety symptoms								
Overall direct effect	0.080	-0.417; 0.576	0.30	0.79	0.157	-0.288; 0.614	0.27	0.57
Overall indirect effect	-0.047	-0.106; 0.007	0.04	0.18	-0.052	-0.122; 0.007	0.04	0.19
Total effect	0.034	-0.460; 0.530	0.30	0.91	0.105	-0.336; 0.558	0.27	0.70

Note: β = Mean difference, which is the difference in mean Patient Health Questionnaire-9/Generalized Anxiety Disorder-7 score at 12 months, when comparing the intervention groups to the standard of care; CI: confidence interval; SE: standard error.

REFERENCES

1. Edmiston N, Passmore E, Smith DJ, Petoumenos K. Multimorbidity among people with HIV in regional New South Wales, Australia. *Sexual health.* 2015;12(5):425-432.
2. Kendall CE, Wong J, Taljaard M, et al. A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario. *BMC public health.* 2014;14:161.
3. Adams C, Zacharia S, Masters L, Coffey C, Catalan P. Mental health problems in people living with HIV: changes in the last two decades: the London experience 1990-2014. *AIDS care.* 2016;28 Suppl 1(sup1):56-59.
4. Gaynes BN, Pence BW, Eron JJ, Jr., Miller WC. Prevalence and comorbidity of psychiatric diagnoses based on reference standard in an HIV+ patient population. *Psychosomatic medicine.* 2008;70(4):505-511.
5. Pence BW, Miller WC, Whetten K, Eron JJ, Gaynes BN. Prevalence of DSM-IV-defined mood, anxiety, and substance use disorders in an HIV clinic in the Southeastern United States. *Journal of acquired immune deficiency syndromes (1999).* 2006;42(3):298-306.
6. Nakimuli-Mpungu E, Bass JK, Alexandre P, et al. Depression, alcohol use and adherence to antiretroviral therapy in sub-Saharan Africa: a systematic review. *AIDS and behavior.* 2012;16(8):2101-2118.
7. Nel A, Kagee A. Common mental health problems and antiretroviral therapy adherence. *AIDS Care.* 2011;23(11):1360-1365.
8. Tao J, Qian HZ, Kipp AM, et al. Effects of depression and anxiety on antiretroviral therapy adherence among newly diagnosed HIV-infected Chinese MSM. *AIDS (London, England).* 2017;31(3):401-406.
9. Ickovics JR, Hamburger ME, Vlahov D, et al. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. *Jama.* 2001;285(11):1466-1474.
10. Leserman J, Jackson ED, Petitto JM, et al. Progression to AIDS: the effects of stress, depressive symptoms, and social support. *Psychosomatic medicine.* 1999;61(3):397-406.
11. Mirani G, Williams PL, Chernoff M, et al. Changing Trends in Complications and Mortality Rates Among US Youth and Young Adults With HIV Infection in the Era of Combination Antiretroviral Therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;61(12):1850-1861.
12. Pence BW, Miller WC, Gaynes BN, Eron JJ, Jr. Psychiatric illness and virologic response in patients initiating highly active antiretroviral therapy. *Journal of acquired immune deficiency syndromes (1999).* 2007;44(2):159-166.
13. Rivera-Rivera Y, Vazquez-Santiago FJ, Albino E, Sanchez MD, Rivera-Amill V. Impact of Depression and Inflammation on the Progression of HIV Disease. *Journal of clinical & cellular immunology.* 2016;7(3).

14. Silverberg MJ, Leyden WA, Leibowitz A, et al. Factors associated with hazardous alcohol use and motivation to reduce drinking among HIV primary care patients: Baseline findings from the Health & Motivation study. *Addictive behaviors.* 2018;84:110-117.

15. Reid MC, Fiellin DA, O'Connor PG. Hazardous and harmful alcohol consumption in primary care. *Archives of internal medicine.* 1999;159(15):1681-1689.

16. Chander G, Lau B, Moore RD. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. *Journal of acquired immune deficiency syndromes (1999).* 2006;43(4):411-417.

17. Marshall BDL, Tate JP, McGinnis KA, et al. Long-term alcohol use patterns and HIV disease severity. *AIDS (London, England).* 2017;31(9):1313-1321.

18. ALLAN CA. ALCOHOL PROBLEMS AND ANXIETY DISORDERS—A CRITICAL REVIEW. *Alcohol and Alcoholism.* 1995;30(2):145-151.

19. Fergusson DM, Boden JM, Horwood LJ. Tests of Causal Links Between Alcohol Abuse or Dependence and Major Depression. *JAMA Psychiatry.* 2009;66(3):260-266.

20. Hasin DS, Grant BF. Major depression in 6050 former drinkers: association with past alcohol dependence. *Arch Gen Psychiatry.* 2002;59(9):794-800.

21. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. *Clinical psychology review.* 2000;20(2):149-171.

22. Braithwaite RS, Fang Y, Tate J, et al. Do Alcohol Misuse, Smoking, and Depression Vary Concordantly or Sequentially? A Longitudinal Study of HIV-Infected and Matched Uninfected Veterans in Care. *AIDS and behavior.* 2016;20(3):566-572.

23. Fojo AT, Lesko CR, Calkins KL, et al. Do Symptoms of Depression Interact with Substance Use to Affect HIV Continuum of Care Outcomes? *AIDS and behavior.* 2019;23(3):580-591.

24. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of Mental Disorders With Alcohol and Other Drug Abuse: Results From the Epidemiologic Catchment Area (ECA) Study. *Jama.* 1990;264(19):2511-2518.

25. Anastos K, Schneider MF, Gange SJ, et al. The association of race, sociodemographic, and behavioral characteristics with response to highly active antiretroviral therapy in women. *Journal of acquired immune deficiency syndromes (1999).* 2005;39(5):537-544.

26. Ironson G, O'Cleirigh C, Fletcher MA, et al. Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment. *Psychosomatic medicine.* 2005;67(6):1013-1021.

27. Parienti JJ, Massari V, Descamps D, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2004;38(9):1311-1316.

28. Chander G, Hutton HE, Lau B, Xu X, McCaul ME. Brief Intervention Decreases Drinking Frequency in HIV-Infected, Heavy Drinking Women: Results of a Randomized Controlled Trial. *Journal of acquired immune deficiency syndromes (1999).* 2015;70(2):137-145.

29. Naar-King S, Wright K, Parsons JT, et al. Healthy choices: motivational enhancement therapy for health risk behaviors in HIV-positive youth. *AIDS education and prevention : official publication of the International Society for AIDS Education.* 2006;18(1):1-11.

30. Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. *Journal of acquired immune deficiency syndromes (1999).* 2007;46(4):443-450.

31. Miller WR. Motivational enhancement therapy with drug abusers. 1995.

32. Ann Vernon KAD. *Cognitive Behavior Therapies: A guidebook for practitioners.* 2018.

33. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Archives of internal medicine.* 1998;158(16):1789-1795.

34. World Health Organization. *Depression and other common health disorders: Global Health Estimates.* Geneva2017.

35. Association AP. *DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.* Washington, DC: American Psychiatric Association; 2013.

36. Collaborators GDaIIaP. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England).* 2016;388(10053):1545-1602.

37. World Health Organization. *Global Health Estimates 2016: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2016.* Geneva2018.

38. Ewald Horwath FG, Myrna M. Weissman. Epidemiology of anxiety disorders. In: Ming T. Tsuang Mauricio Tohen PBJ, ed. *Textbook of Psychiatric Epidemiology, Third Edition.* Wiley-Blackwell; 2011:311-328.

39. Chipimo PJ, Fylkesnes K. Mental distress in the general population in Zambia: impact of HIV and social factors. *BMC public health.* 2009;9:298.

40. Kee MK, Lee SY, Kim NY, et al. Anxiety and depressive symptoms among patients infected with human immunodeficiency virus in South Korea. *AIDS Care.* 2015;27(9):1174-1182.

41. Maj M, Janssen R, Starace F, et al. WHO Neuropsychiatric AIDS study, cross-sectional phase I. Study design and psychiatric findings. *Arch Gen Psychiatry.* 1994;51(1):39-49.

42. Moore CL, Grulich AE, Prestage G, et al. Hospitalization for Anxiety and Mood Disorders in HIV-Infected and -Uninfected Gay and Bisexual Men. *Journal of acquired immune deficiency syndromes (1999).* 2016;73(5):589-597.

43. Jallow A, Ljunggren G, Wandell P, Carlsson AC. Prevalence, incidence, mortality and co-morbidities amongst human immunodeficiency virus (HIV) patients in Stockholm County, Sweden - the Greater Stockholm HIV Cohort Study. *AIDS Care.* 2015;27(2):142-149.

44. Conover CJ, Arno P, Weaver M, Ang A, Ettner SL. Income and employment of people living with combined HIV/AIDS, chronic mental illness, and substance abuse disorders. *The journal of mental health policy and economics.* 2006;9(2):71-86.

45. Larios SE, Davis JN, Gallo LC, Heinrich J, Talavera G. Concerns about stigma, social support and quality of life in low-income HIV-positive Hispanics. *Ethnicity & disease.* 2009;19(1):65-70.

46. Stutterheim SE, Bos AE, Pryor JB, Brands R, Liebregts M, Schaalma HP. Psychological and social correlates of HIV status disclosure: the significance of stigma visibility. *AIDS education and prevention : official publication of the International Society for AIDS Education.* 2011;23(4):382-392.

47. Thomas BE, Rehman F, Suryanarayanan D, et al. How stigmatizing is stigma in the life of people living with HIV: a study on HIV positive individuals from Chennai, South India. *AIDS Care.* 2005;17(7):795-801.

48. Yu NX, Zhang J, Chan CL. Health Care Neglect, Perceived Discrimination, and Dignity-Related Distress Among Chinese Patients With HIV. *AIDS education and prevention : official publication of the International Society for AIDS Education.* 2016;28(1):90-102.

49. Collins PY, Holman AR, Freeman MC, Patel V. What is the relevance of mental health to HIV/AIDS care and treatment programs in developing countries? A systematic review. *AIDS (London, England).* 2006;20(12):1571-1582.

50. Lin WC, Chou KH, Chen HL, et al. Structural deficits in the emotion circuit and cerebellum are associated with depression, anxiety and cognitive dysfunction in methadone maintenance patients: a voxel-based morphometric study. *Psychiatry research.* 2012;201(2):89-97.

51. Norman LR, Basso M. An Update of the Review of Neuropsychological Consequences of HIV and Substance Abuse: A Literature Review and Implications for Treatment and Future Research. *Current drug abuse reviews.* 2015;8(1):50-71.

52. Del Guerra FB, Fonseca JL, Figueiredo VM, Ziff EB, Konkiewitz EC. Human immunodeficiency virus-associated depression: contributions of immuno-inflammatory, monoaminergic, neurodegenerative, and neurotrophic pathways. *Journal of neurovirology.* 2013;19(4):314-327.

53. Eller LS, Rivero-Mendez M, Voss J, et al. Depressive symptoms, self-esteem, HIV symptom management self-efficacy and self-compassion in people living with HIV. *AIDS Care.* 2014;26(7):795-803.

54. L'akoa RM, Noubiap JJN, Fang Y, Ntone FE, Kuaban C. Prevalence and correlates of depressive symptoms in HIV-positive patients: a cross-sectional study among newly diagnosed patients in Yaoundé, Cameroon. *BMC psychiatry.* 2013;13(1):228.

55. Williams AB, Wang H, Li X, Chen J, Li L, Fennie K. Efficacy of an Evidence-Based ARV Adherence Intervention in China. *AIDS Patient Care STDS.* 2014;28(8):411-417.

56. Bing EG, Burnam MA, Longshore D, et al. Psychiatric Disorders and Drug Use Among Human Immunodeficiency Virus–Infected Adults in the United States. *Archives of General Psychiatry.* 2001;58(8):721-728.

57. Hellmuth J, Colby D, Valcour V, et al. Depression and Anxiety are Common in Acute HIV Infection and Associate with Plasma Immune Activation. *AIDS and behavior.* 2017;21(11):3238-3246.

58. Tesfaw G, Ayano G, Awoke T, et al. Prevalence and correlates of depression and anxiety among patients with HIV on-follow up at Alert Hospital, Addis Ababa, Ethiopia. *BMC psychiatry.* 2016;16(1):368.

59. Williams P, Narciso L, Browne G, Roberts J, Weir R, Gafni A. The prevalence, correlates, and costs of depression in people living with HIV/AIDS in Ontario: implications for service directions. *AIDS education and prevention : official publication of the International Society for AIDS Education.* 2005;17(2):119-130.

60. Lopes M, Olfson M, Rabkin J, et al. Gender, HIV status, and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of clinical psychiatry.* 2012;73(3):384-391.

61. Catalan J, Meadows J, Douzenis A. The changing pattern of mental health problems in HIV infection: the view from London, UK. *AIDS Care.* 2000;12(3):333-341.

62. Powers C, Comfort M, Lopez AM, Kral AH, Murdoch O, Lorvick J. Addressing Structural Barriers to HIV Care among Triply Diagnosed Adults: Project Bridge Oakland. *Health & social work.* 2017;42(2):e53-e61.

63. Reece M. HIV-related mental health care: factors influencing dropout among low-income, HIV-positive individuals. *AIDS Care.* 2003;15(5):707-716.

64. Remien RH, Stirratt MJ, Nguyen N, Robbins RN, Pala AN, Mellins CA. Mental health and HIV/AIDS: the need for an integrated response. *AIDS (London, England).* 2019;33(9):1411-1420.

65. Watt N, Sigfrid L, Legido-Quigley H, et al. Health systems facilitators and barriers to the integration of HIV and chronic disease services: a systematic review. *Health policy and planning.* 2017;32(suppl_4):iv13-iv26.

66. Esposito CA, Steel Z, Gioi TM, Huyen TTN, Tarantola D. The prevalence of depression among men living with HIV infection in Vietnam. *Am J Public Health.* 2009;99 Suppl 2(Suppl 2):S439-S444.

67. Abas M, Ali G-C, Nakimuli-Mpungu E, Chibanda D. Depression in people living with HIV in sub-Saharan Africa: time to act. *Tropical Medicine & International Health.* 2014;19(12):1392-1396.

68. Bernard C, Dabis F, de Rekeneire N. Prevalence and factors associated with depression in people living with HIV in sub-Saharan Africa: A systematic review and meta-analysis. *PloS one.* 2017;12(8):e0181960.

69. Kinyanda E, Hoskins S, Nakku J, Nawaz S, Patel V. The prevalence and characteristics of suicidality in HIV/AIDS as seen in an African population in Entebbe district, Uganda. *BMC psychiatry.* 2012;12:63.

70. Ormel J, VonKorff M, Ustun TB, Pini S, Korten A, Oldehinkel T. Common mental disorders and disability across cultures. Results from the WHO Collaborative Study on Psychological Problems in General Health Care. *Jama.* 1994;272(22):1741-1748.

71. Uthman OA, Magidson JF, Safren SA, Nachega JB. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis. *Current HIV/AIDS reports.* 2014;11(3):291-307.

72. Wykowski J, Kemp CG, Velloza J, Rao D, Drain PK. Associations Between Anxiety and Adherence to Antiretroviral Medications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *AIDS and behavior.* 2019.

73. Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. *Journal of acquired immune deficiency syndromes (1999).* 2011;58(2):181-187.

74. Gonzalez JS, Psaros C, Batchelder A, Applebaum A, Newville H, Safren SA. Clinician-assessed depression and HAART adherence in HIV-infected individuals in methadone maintenance treatment. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine.* 2011;42(1):120-126.

75. Tucker JS, Orlando M, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Psychosocial mediators of antiretroviral nonadherence in HIV-positive adults with substance use and mental health problems. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 2004;23(4):363-370.

76. Weaver KE, Llabre MM, Duran RE, et al. A stress and coping model of medication adherence and viral load in HIV-positive men and women on highly active antiretroviral therapy (HAART). *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 2005;24(4):385-392.

77. Shrestha R, Copenhaver MM. Viral suppression among HIV-infected methadone-maintained patients: The role of ongoing injection drug use and adherence to antiretroviral therapy (ART). *Addictive behaviors.* 2018;85:88-93.

78. Kingori C, Haile ZT, Ngatia P. Depression symptoms, social support and overall health among HIV-positive individuals in Kenya. *International journal of STD & AIDS.* 2015;26(3):165-172.

79. Nanni MG, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV Infected Patients: a Review. *Current Psychiatry Reports.* 2014;17(1):530.

80. Ironson G, O'Cleirigh C, Kumar M, et al. Psychosocial and Neurohormonal Predictors of HIV Disease Progression (CD4 Cells and Viral Load): A 4 Year Prospective Study. *AIDS and behavior.* 2015;19(8):1388-1397.

81. Nance RM, Delaney JAC, Simoni JM, et al. HIV Viral Suppression Trends Over Time Among HIV-Infected Patients Receiving Care in the United States, 1997 to 2015: A Cohort Study. *Ann Intern Med.* 2018;169(6):376-384.

82. Pence BW, Mills JC, Bengtson AM, et al. Association of Increased Chronicity of Depression With HIV Appointment Attendance, Treatment Failure, and Mortality Among HIV-Infected Adults in the United States. *JAMA psychiatry.* 2018;75(4):379-385.

83. Amirkhanian YA, Kelly JA, DiFranceisco WJ, et al. Predictors of HIV Care Engagement, Antiretroviral Medication Adherence, and Viral Suppression Among People Living with HIV Infection in St. Petersburg, Russia. *AIDS and behavior.* 2018;22(3):791-799.

84. Bucek A, Leu C-S, Benson S, et al. Psychiatric Disorders, Antiretroviral Medication Adherence and Viremia in a Cohort of Perinatally HIV-Infected Adolescents and Young Adults. *Pediatr Infect Dis J.* 2018;37(7):673-677.

85. Shacham E, Morgan JC, Önen NF, Taniguchi T, Overton ET. Screening anxiety in the HIV clinic. *AIDS and behavior.* 2012;16(8):2407-2413.

86. World Health Organization. *Global status report on alcohol and health 2018.* Geneva2018.

87. Thomas F. Babor JCH-B, John B. Saunders, Maristela G. Monteiro. *The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Care.* Geneva2001.

88. National Institute on Alcohol Abuse and Alcoholism. *The Physicians' Guide to Helping Patients With Alcohol Problems.* Washington: DC Government Printing Office; 1995.

89. National Collaborating Centre for Mental Health (UK). Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. Leicester (UK): British Psychological Society; 2011. (NICE Clinical Guidelines, No. 115.) 2, ALCOHOL DEPENDENCE AND HARMFUL ALCOHOL USE. In:2011.

90. Veld DHI, Pengpid S, Colebunders R, Skaal L, Peltzer K. High-risk alcohol use and associated socio-demographic, health and psychosocial factors in patients with HIV infection in three primary health care clinics in South Africa. *International journal of STD & AIDS.* 2017;28(7):651-659.

91. da Silva CM, Mendoza-Sassi RA, da Mota LD, Nader MM, de Martinez AM. Alcohol use disorders among people living with HIV/AIDS in Southern Brazil: prevalence, risk factors and biological markers outcomes. *BMC infectious diseases.* 2017;17(1):263.

92. Galvan FH, Bing EG, Fleishman JA, et al. The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study. *Journal of studies on alcohol.* 2002;63(2):179-186.

93. Reis RK, Melo ES, Gir E. Factors associated with inconsistent condom use among people living with HIV/Aids. *Revista brasileira de enfermagem.* 2016;69(1):40-46.

94. Fromme K, D'Amico EJ, Katz EC. Intoxicated sexual risk taking: an expectancy or cognitive impairment explanation? *Journal of studies on alcohol.* 1999;60(1):54-63.

95. MacDonald TK, MacDonald G, Zanna MP, Fong GT. Alcohol, sexual arousal, and intentions to use condoms in young men: applying alcohol myopia theory to risky sexual behavior. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 2000;19(3):290-298.

96. Sales JM, Brown JL, Vissman AT, DiClemente RJ. The association between alcohol use and sexual risk behaviors among African American women across three developmental periods: a review. *Current drug abuse reviews.* 2012;5(2):117-128.

97. Cook RL, Sereika SM, Hunt SC, Woodward WC, Erlen JA, Conigliaro J. Problem drinking and medication adherence among persons with HIV infection. *Journal of general internal medicine.* 2001;16(2):83-88.

98. Gross R, Bellamy SL, Ratshaa B, et al. Effects of sex and alcohol use on antiretroviral therapy outcomes in Botswana: a cohort study. *Addiction (Abingdon, England).* 2017;112(1):73-81.

99. Hendershot CS, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence: review and meta-analysis. *Journal of acquired immune deficiency syndromes (1999).* 2009;52(2):180-202.

100. McCance-Katz EF, Gruber VA, Beatty G, Lum PJ, Rainey PM. Interactions between alcohol and the antiretroviral medications ritonavir or efavirenz. *Journal of addiction medicine.* 2013;7(4):264-270.

101. Bilal U, Lau B, Lazo M, et al. Interaction Between Alcohol Consumption Patterns, Antiretroviral Therapy Type, and Liver Fibrosis in Persons Living with HIV. *AIDS Patient Care STDS.* 2016;30(5):200-207.

102. Shuper PA, Neuman M, Kanteres F, Baliunas D, Joharchi N, Rehm J. Causal considerations on alcohol and HIV/AIDS--a systematic review. *Alcohol and alcoholism (Oxford, Oxfordshire).* 2010;45(2):159-166.

103. Kader R, Seedat S, Govender R, Koch JR, Parry CD. Hazardous and harmful use of alcohol and/or other drugs and health status among South African patients attending HIV clinics. *AIDS and behavior.* 2014;18(3):525-534.

104. Marcellin F, Lions C, Winnock M, et al. Self-reported alcohol abuse in HIV-HCV co-infected patients: a better predictor of HIV virological rebound than physician's perceptions (HEPAVIH ARNS CO13 cohort). *Addiction (Abingdon, England).* 2013;108(7):1250-1258.

105. Shacham E, Agbebi A, Stamm K, Overton ET. Alcohol consumption is associated with poor health in HIV clinic patient population: a behavioral surveillance study. *AIDS and behavior.* 2011;15(1):209-213.

106. Vagenas P, Azar MM, Copenhaver MM, Springer SA, Molina PE, Altice FL. The Impact of Alcohol Use and Related Disorders on the HIV Continuum of Care: a Systematic Review : Alcohol and the HIV Continuum of Care. *Current HIV/AIDS reports.* 2015;12(4):421-436.

107. George DT, Nutt DJ, Dwyer BA, Linnoila M. Alcoholism and panic disorder: is the comorbidity more than coincidence? *Acta psychiatrica Scandinavica.* 1990;81(2):97-107.

108. Sullivan LE, Goulet JL, Justice AC, Fiellin DA. Alcohol consumption and depressive symptoms over time: a longitudinal study of patients with and without HIV infection. *Drug and alcohol dependence.* 2011;117(2-3):158-163.

109. Paulus DJ, Jardin C, Bakhshaie J, et al. Anxiety sensitivity and hazardous drinking among persons living with HIV/AIDS: An examination of the role of emotion dysregulation. *Addictive behaviors.* 2016;63:141-148.

110. Longmire-Avital B, Holder CA, Golub SA, Parsons JT. Risk factors for drinking among HIV-positive African American adults: the depression-gender interaction. *The American journal of drug and alcohol abuse.* 2012;38(3):260-266.

111. Palfai TP, Cheng DM, Coleman SM, Bridden C, Krupitsky E, Samet JH. The influence of depressive symptoms on alcohol use among HIV-infected Russian drinkers. *Drug and alcohol dependence.* 2014;134:85-91.

112. World Health Organization. Number of people (all ages) living with HIV: Estimates by WHO region. 2018; http://apps.who.int/gho/data/view.main.22100WHO?lang=en. Accessed July 3, 2019.

113. Canan CE, Lau B, McCaul ME, Keruly J, Moore RD, Chander G. Effect of alcohol consumption on all-cause and liver-related mortality among HIV-infected individuals. *HIV medicine.* 2017;18(5):332-341.

114. Blashill AJ, Bedoya CA, Mayer KH, et al. Psychosocial Syndemics are Additively Associated with Worse ART Adherence in HIV-Infected Individuals. *AIDS and behavior.* 2015;19(6):981-986.

115. Friedman MR, Stall R, Silvestre AJ, et al. Effects of syndemics on HIV viral load and medication adherence in the multicentre AIDS cohort study. *AIDS (London, England).* 2015;29(9):1087-1096.

116. Harkness A, Bainter SA, O'Cleirigh C, Mendez NA, Mayer KH, Safren SA. Longitudinal Effects of Syndemics on ART Non-adherence Among Sexual Minority Men. *AIDS and behavior.* 2018;22(8):2564-2574.

117. Kuhns LM, Hotton AL, Garofalo R, et al. An Index of Multiple Psychosocial, Syndemic Conditions Is Associated with Antiretroviral Medication Adherence Among HIV-Positive Youth. *AIDS Patient Care STDS.* 2016;30(4):185-192.

118. Brown JL, DeMartini KS, Sales JM, Swartzendruber AL, DiClemente RJ. Interventions to reduce alcohol use among HIV-infected individuals: a review and critique of the literature. *Current HIV/AIDS reports.* 2013;10(4):356-370.

119. Miller WR, Rollnick S. *Motivational Interviewing : Helping People Change.* New York, UNITED STATES: Guilford Publications; 2012.

120. Vernon A, Doyle KA. *Cognitive Behavior Therapies--Basics and Beyond : A Guidebook for Counselors.* Newark, UNITED STATES: American Counseling Association; 2017.

121. Scott-Sheldon LAJ, Carey KB, Johnson BT, Carey MP. Behavioral Interventions Targeting Alcohol Use Among People Living with HIV/AIDS: A Systematic Review and Meta-Analysis. *AIDS and behavior.* 2017;21(Suppl 2):126-143.

122. Charlet K, Heinz A. Harm reduction—a systematic review on effects of alcohol reduction on physical and mental symptoms. *Addiction Biology.* 2017;22(5):1119-1159.

123. Shaw GK, Waller S, Latham CJ, Dunn G, Thomson AD. The detoxification experience of alcoholic in-patients and predictors of outcome. *Alcohol and alcoholism (Oxford, Oxfordshire).* 1998;33(3):291-303.

124. United Nations. Vietnam - Country profile. 2018; http://data.un.org/en/iso/vn.html. Accessed July 9, 2019.

125. United Nations. Vietnam at a glance. http://www.un.org.vn/en/about-viet-nam/overview.html. Accessed July 9, 2019.

126. World Bank. The World Bank in Vietnam - Overview. 2019; https://www.worldbank.org/en/country/vietnam/overview. Accessed July 9, 2019.

127. Takashima K, Wada K, Tra TT, Smith DR. A review of Vietnam's healthcare reform through the Direction of Healthcare Activities (DOHA). *Environ Health Prev Med.* 2017;22(1):74-74.

128. World Bank. Life expetancy at birth, total: Vietnam. 2017; https://data.worldbank.org/indicator/SP.DYN.LE00.IN?locations=VN&view=chart. Accessed July 9, 2019.

129. Vietnam Authority for AIDS Control. *An annual update on the HIV epidemic in Vietnam.* Hanoi2014.

130. UNAIDS. Country factsheets: Vietnam. 2018; https://www.unaids.org/en/regionscountries/countries/vietnam. Accessed August 12, 2019.

131. García MC, Meyer SB, Ward P. Elevated HIV prevalence and risk behaviours among men who have sex with men (MSM) in Vietnam: a systematic review. *BMJ open.* 2012;2(5):e001511.

132. Downie R. *Advancing Country Partnerships on HIV/AIDS.* 2017.

133. Nguyen QLT, Van Phan T, Tran BX, et al. Health insurance for patients with HIV/AIDS in Vietnam: coverage and barriers. *BMC Health Serv Res.* 2017;17(1):519-519.

134. UNAIDS. *Ending AIDS: Progress towards the 90-90-90 targets.* 2017.

135. Lee SJ, Li L, Lin C, Tuan le A. Challenges facing HIV-positive persons who use drugs and their families in Vietnam. *AIDS Care.* 2015;27(3):283-287.

136. Lim TW, Frangakis C, Latkin C, et al. Community-level income inequality and HIV prevalence among persons who inject drugs in Thai Nguyen, Vietnam. *PloS one.* 2014;9(3):e90723.

137. Tran BX, Nguyen N, Ohinmaa A, et al. Prevalence and correlates of alcohol use disorders during antiretroviral treatment in injection-driven HIV epidemics in Vietnam. *Drug and alcohol dependence.* 2013;127(1-3):39-44.

138. Van Nguyen H, Nguyen HL, Mai HT, et al. Stigmatization among methadone maintenance treatment patients in mountainous areas in northern Vietnam. *Harm reduction journal.* 2017;14(1):1.

139. Giang KB, Van Minh H, Allebeck P. Alcohol consumption and household expenditure on alcohol in a rural district in Vietnam. *Glob Health Action.* 2013;6:18937-18937.

140. Lincoln M. Alcohol and drinking cultures in Vietnam: A review. *Drug and alcohol dependence.* 2016;159:1-8.

141. Van Bui T, Blizzard CL, Luong KN, et al. Alcohol Consumption in Vietnam, and the Use of 'Standard Drinks' to Measure Alcohol Intake. *Alcohol and Alcoholism.* 2015;51(2):186-195.

142. World Health Organization. *Global Status Report on Alcohol and Health 2014.* Geneva2014.

143. Hershow RB, Zuskov DS, Vu Tuyet Mai N, et al. "[Drinking is] Like a Rule That You Can't Break": Perceived Barriers and Facilitators to Reduce Alcohol Use and Improve Antiretroviral Treatment Adherence among People Living with HIV and Alcohol Use Disorder in Vietnam. *Subst Use Misuse.* 2018;53(7):1084-1092.

144. Luu BN, Nguyen TT, Newman IM. Traditional alcohol production and use in three provinces in Vietnam: an ethnographic exploration of health benefits and risks. *BMC public health.* 2014;14:731.

145. Thai TT, Jones MK, Harris LM, Heard RC. The association between symptoms of mental disorders and health risk behaviours in Vietnamese HIV positive outpatients: a cross-sectional study. *BMC public health.* 2017;17(1):250.

146. Levintow SN, Pence BW, Ha TV, et al. Prevalence and predictors of depressive symptoms among HIV-positive men who inject drugs in Vietnam. *PloS one.* 2018;13(1):e0191548.

147. Hershow RB, Miller WC, Giang LM, et al. Minority Stress and Experience of Sexual Violence Among Men Who Have Sex With Men in Hanoi, Vietnam: Results From a Cross-Sectional Study. *Journal of interpersonal violence.* 2018:886260518819884.

148. Levintow SN, Pence BW, Ha TV, et al. Depressive Symptoms at HIV Testing and Two-Year All-Cause Mortality Among Men Who Inject Drugs in Vietnam. *AIDS and behavior.* 2019;23(3):609-616.

149. Tran BX, Dang AK, Truong NT, et al. Depression and Quality of Life among Patients Living with HIV/AIDS in the Era of Universal Treatment Access in Vietnam. *International journal of environmental research and public health.* 2018;15(12).

150. Bystritsky A, Kronemyer D. Stress and anxiety: counterpart elements of the stress/anxiety complex. *The Psychiatric clinics of North America.* 2014;37(4):489-518.

151. Hammen C. Stress and depression. *Annual review of clinical psychology.* 2005;1:293-319.

152. Dean J, Keshavan M. The neurobiology of depression: An integrated view. *Asian journal of psychiatry.* 2017;27:101-111.

153. Karen Glanz BKR, K. Viswanath. Health behavior and health education: Theory, Research and Practice. 2008.

154. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. *Nature reviews Immunology.* 2005;5(3):243-251.

155. Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology.* 2006;1(4):421-427.

156. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *The New England journal of medicine.* 1991;325(9):606-612.

157. Kiecolt-Glaser JK, Glaser R, Shuttleworth EC, Dyer CS, Ogrocki P, Speicher CE. Chronic stress and immunity in family caregivers of Alzheimer's disease victims. *Psychosomatic medicine.* 1987;49(5):523-535.

158. Evans DL, Ten Have TR, Douglas SD, et al. Association of depression with viral load, CD8 T lymphocytes, and natural killer cells in women with HIV infection. *The American journal of psychiatry.* 2002;159(10):1752-1759.

159. Burack JH, Barrett DC, Stall RD, Chesney MA, Ekstrand ML, Coates TJ. Depressive symptoms and CD4 lymphocyte decline among HIV-infected men. *Jama.* 1993;270(21):2568-2573.

160. Lynn C, Chenneville T, Bradley-Klug K, Walsh ASJ, Dedrick RF, Rodriguez CA. Depression, anxiety, and posttraumatic stress as predictors of immune functioning: differences between youth with behaviorally and perinatally acquired HIV. *AIDS Care.* 2019:1-10.

161. Antoni MH, Carrico AW, Duran RE, et al. Randomized clinical trial of cognitive behavioral stress management on human immunodeficiency virus viral load in gay men treated with highly active antiretroviral therapy. *Psychosomatic medicine.* 2006;68(1):143-151.

162. Carrico AW, Antoni MH, Duran RE, et al. Reductions in depressed mood and denial coping during cognitive behavioral stress management with HIV-Positive gay men treated with HAART. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine.* 2006;31(2):155-164.

163. Cruess DG, Antoni MH, Kumar M, et al. Cognitive-behavioral stress management buffers decreases in dehydroepiandrosterone sulfate (DHEA-S) and increases in the cortisol/DHEA-S ratio and reduces mood disturbance and perceived stress among HIV-seropositive men. *Psychoneuroendocrinology.* 1999;24(5):537-549.

164. Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. *Lancet (London, England).* 2017;389(10072):941-950.

165. Singer M. A dose of drugs, a touch of violence, a case of AIDS: conceptualizing the SAVA syndemic. *Free Inquiry - Special Issue: Gangs, Drugs & Violence.* 1996;24(2):99-110.

166. Singer M. *Introduction to Syndemics : A Critical Systems Approach to Public and Community Health.* New York, NY, UNITED STATES: John Wiley & Sons, Incorporated; 2009.

167. McClelland RS, Lavreys L, Katingima C, et al. Contribution of HIV-1 infection to acquisition of sexually transmitted disease: a 10-year prospective study. *The Journal of infectious diseases.* 2005;191(3):333-338.

168. Rueda S, Mitra S, Chen S, et al. Examining the associations between HIV-related stigma and health outcomes in people living with HIV/AIDS: a series of meta-analyses. *BMJ open.* 2016;6(7):e011453.

169. Murphy PJ, Garrido-Hernansaiz H, Mulcahy F, Hevey D. HIV-related stigma and optimism as predictors of anxiety and depression among HIV-positive men who have sex with men in the United Kingdom and Ireland. *AIDS Care.* 2018;30(9):1173-1179.

170. Lunze K, Lioznov D, Cheng DM, et al. HIV Stigma and Unhealthy Alcohol Use Among People Living with HIV in Russia. *AIDS and behavior.* 2017;21(9):2609-2617.

171. Friedman MR, Stall R, Silvestre AJ, et al. Effects of syndemics on HIV viral load and medication adherence in the multicentre AIDS cohort study. *AIDS (London, England).* 2015;29(9):1087-1096.

172. Tsai AC, Burns BF. Syndemics of psychosocial problems and HIV risk: A systematic review of empirical tests of the disease interaction concept. *Social science & medicine (1982).* 2015;139:26-35.

173. van den Berg JJ, Isabel Fernández M, Fava JL, et al. Using Syndemics Theory to Investigate Risk and Protective Factors Associated with Condomless Sex Among Youth Living with HIV in 17 U.S. Cities. *AIDS and behavior.* 2017;21(3):833-844.

174. Wilson PA, Nanin J, Amesty S, Wallace S, Cherenack EM, Fullilove R. Using syndemic theory to understand vulnerability to HIV infection among Black and Latino men in New York City. *J Urban Health.* 2014;91(5):983-998.

175. Beck AT. *Cognitive therapy and the emotional disorders.* New York : International Universities Press, c1976.; 1976.

176. Ellis A. *Reason and emotion in psychotherapy.* Oxford, England: Lyle Stuart; 1962.

177. Clark David A. PD, Hollifield Michael MD, Leahy Robert PD, Beck Judith S. PD. Theory of Cognitive Therapy. In: *Textbook of Psychotherapeutic Treatments.*

178. McHugh RK, Hearon BA, Otto MW. Cognitive behavioral therapy for substance use disorders. *The Psychiatric clinics of North America.* 2010;33(3):511-525.

179. Magill M, Ray LA. Cognitive-behavioral treatment with adult alcohol and illicit drug users: a meta-analysis of randomized controlled trials. *Journal of studies on alcohol and drugs.* 2009;70(4):516-527.

180. Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. *Alcoholism, clinical and experimental research.* 1998;22(6):1300-1311.

181. Miller WR. Motivational Interviewing with Problem Drinkers. *Behavioural Psychotherapy.* 1983;11(2):147-172.

182. Miller WR, Taylor CA, West J. Focused versus broad-spectrum behavior therapy for problem drinkers. *Journal of consulting and clinical psychology.* 1980;48(5):590-601.

183. Miller WR, Rose GS. Toward a theory of motivational interviewing. *Am Psychol.* 2009;64(6):527-537.

184. Festinger L. *A theory of cognitive dissonance.* Stanford: Stanford University Press; 1957.

185. Draycott S, Dabbs A. Cognitive dissonance. 2: A theoretical grounding of motivational interviewing. *The British journal of clinical psychology.* 1998;37(3):355-364.

186. Bem DJ. Self-perception: An alternative interpretation of cognitive dissonance phenomena. *Psychological review.* 1967;74(3):183-200.

187. Britton PC, Patrick H, Wenzel A, Williams GC. Integrating Motivational Interviewing and Self Determination Theory with Cognitive Behavioral Therapy to Prevent Suicide. *Cognitive and behavioral practice.* 2011;18(1):16-27.

188. Christopher PJ, Dougher MJ. A behavior-analytic account of motivational interviewing. *Behav Anal.* 2009;32(1):149-161.

189. Keeley RD, Burke BL, Brody D, et al. Training to Use Motivational Interviewing Techniques for Depression: A Cluster Randomized Trial. *The Journal of the American Board of Family Medicine.* 2014;27(5):621.

190. Keeley RD, Brody DS, Engel M, et al. Motivational interviewing improves depression outcome in primary care: A cluster randomized trial. *Journal of consulting and clinical psychology.* 2016;84(11):993-1007.

191. Angus LE, Kagan F. Therapist empathy and client anxiety reduction in motivational interviewing: "She carries with me, the experience". *Journal of clinical psychology.* 2009;65(11):1156-1167.

192. Le AKA. Improving the control of the HIV epidemic. 2017; http://soytethainguyen.gov.vn/detail/news/vi/1/149/340/index.htm. Accessed Oct 25, 2019.

193. Hutton HE, Lancaster KE, Zuskov D, et al. Cultural Adaptation of 2 Evidence-Based Alcohol Interventions for Antiretroviral Treatment Clinic Patients in Vietnam. *Journal of the International Association of Providers of AIDS Care (JIAPAC).* 2019;18:2325958219854368.

194. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine.* 2001;16(9):606-613.

195. Niemi M, Kiel S, Allebeck P, Hoan le T. Community-based intervention for depression management at the primary care level in Ha Nam Province, Vietnam: a cluster-randomised controlled trial. *Tropical medicine & international health : TM & IH.* 2016;21(5):654-661.

196. Vu NTT, Holt M, Phan HTT, et al. Amphetamine-Type-Stimulants (ATS) Use and Homosexuality-Related Enacted Stigma Are Associated With Depression Among Men Who Have Sex With Men (MSM) in Two Major Cities in Vietnam in 2014. *Subst Use Misuse.* 2017;52(11):1411-1419.

197. Chibanda D, Cowan F, Gibson L, Weiss HA, Lund C. Prevalence and correlates of probable common mental disorders in a population with high prevalence of HIV in Zimbabwe. *BMC psychiatry.* 2016;16:55.

198. Lowe B, Decker O, Muller S, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Medical care.* 2008;46(3):266-274.

199. Nguyen MS, Reemann P, Loorits D, et al. Association of Temporomandibular Joint Osseous Changes with Anxiety, Depression, and Limitation of Mandibular Function in Elderly Vietnamese. *East Asian archives of psychiatry : official journal of the Hong Kong College of Psychiatrists = Dong Ya jing shen ke xue zhi : Xianggang jing shen ke yi xue yuan qi kan.* 2019;29(1):20-25.

200. Pollack AA, Weiss B, Trung LT. Mental health, life functioning and risk factors among people exposed to frequent natural disasters and chronic poverty in Vietnam. *BJPsych open.* 2016;2(3):221-232.

201. The PHQ-9: A new depression diagnostic and severity measure [press release]. US: SLACK2002.

202. Maust D, Cristancho M, Gray L, Rushing S, Tjoa C, Thase ME. Chapter 13 - Psychiatric rating scales. In: Aminoff MJ, Boller F, Swaab DF, eds. *Handbook of Clinical Neurology.* Vol 106. Elsevier; 2012:227-237.

203. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine.* 2006;166(10):1092-1097.

204. Schmitz S, Adams R, Walsh C. The use of continuous data versus binary data in MTC models: A case study in rheumatoid arthritis. *BMC Medical Research Methodology.* 2012;12(1):167.

205. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic

psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry.* 1998;59 Suppl 20:22-33;quiz 34-57.

206. Sobell LC, Agrawal S, Annis H, et al. Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline followback and inventory of drinking situations. *Subst Use Misuse.* 2001;36(3):313-331.

207. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug and alcohol dependence.* 1996;42(1):49-54.

208. Cohen J. *Statistical power analysis for the behavioral sciences, 2nd edition.* Routledge; 1988.

209. Ahola K, Hakanen J, Perhoniemi R, Mutanen P. Relationship between burnout and depressive symptoms: A study using the person-centred approach. *Burnout Research.* 2014;1(1):29-37.

210. Kreidler SM, Muller KE, Grunwald GK, et al. GLIMMPSE: Online power computation for linear models with and without a baseline covariate. *Journal of Statistical Software.* 2013;54(10):1-26.

211. Srinivasan R, Pearson RM, Johnson S, Lewis G, Lewis G. Maternal perinatal depressive symptoms and offspring psychotic experiences at 18 years of age: a longitudinal study. *The Lancet Psychiatry.* 2020;7(5):431-440.

212. Hah JM, Hilmoe H, Schmidt P, et al. Preoperative Factors Associated with Remote Postoperative Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort: Post Hoc Analysis of a Perioperative Gabapentin Trial. *Journal of pain research.* 2020;13:2959-2970.

213. Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Statistical methods in medical research.* 2013;22(6):661-670.

214. Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics.* 2001;57(1):120-125.

215. David G. Kleinbaum LLK, Azhar Nizam, Eli S. Rosenberg. *Applied Regression Analysis and Other Multivariable Methods. 5th edition.* USA: Cengage Learning; 2013.

216. Skelly AC, Dettori JR, Brodt ED. Assessing bias: the importance of considering confounding. *Evid Based Spine Care J.* 2012;3(1):9-12.

217. Garrett M. Fitzmaurice NML, James H. Ware. *Applied Longitudinal Analysis, Second Edition.* New Jersey: John Wiley & Sons; 2011.

218. McNeish D, Stapleton LM, Silverman RD. On the unnecessary ubiquity of hierarchical linear modeling. *Psychological methods.* 2017;22(1):114-140.

219. Abas MA, Weiss HA, Simms V, et al. The effect of co-morbid anxiety on remission from depression for people participating in a randomised controlled trial of the Friendship Bench intervention in Zimbabwe. *EClinicalMedicine.* 2020;23.

220. Alzahrani A, Alghamdi A, Alqarni T, Alshareef R, Alzahrani A. Prevalence and predictors of depression, anxiety, and stress symptoms among patients with type II diabetes attending primary healthcare centers in the western region of Saudi Arabia: a cross-sectional study. *International journal of mental health systems.* 2019;13:48.

221. Le TA, Le MQT, Dang AD, et al. Multi-level predictors of psychological problems among methadone maintenance treatment patients in difference types of settings in Vietnam. *Substance abuse treatment, prevention, and policy.* 2019;14(1):39.

222. Paz C, Mascialino G, Adana-Díaz L, et al. Behavioral and sociodemographic predictors of anxiety and depression in patients under epidemiological surveillance for COVID-19 in Ecuador. *PloS one.* 2020;15(9):e0240008.

223. Strauss SM, Rosedale MT, Rindskopf DM. Predictors of Depression Among Adult Women With Diabetes in the United States: An Analysis Using National Health and Nutrition Examination Survey Data From 2007 to 2012. *The Diabetes educator.* 2016;42(6):728-738.

224. Cole DA, Maxwell SE. Testing mediational models with longitudinal data: questions and tips in the use of structural equation modeling. *Journal of abnormal psychology.* 2003;112(4):558-577.

225. Goldsmith KA, MacKinnon DP, Chalder T, White PD, Sharpe M, Pickles A. Tutorial: The practical application of longitudinal structural equation mediation models in clinical trials. *Psychological methods.* 2018;23(2):191-207.

226. Mackinnon DP, Lockwood CM, Williams J. Confidence Limits for the Indirect Effect: Distribution of the Product and Resampling Methods. *Multivariate Behav Res.* 2004;39(1):99-99.

227. Seid S, Abdu O, Mitiku M, Tamirat KS. Prevalence of depression and associated factors among HIV/AIDS patients attending antiretroviral therapy clinic at Dessie referral hospital, South Wollo, Ethiopia. *International journal of mental health systems.* 2020;14(1):55.

228. Mughal AY, Stockton MA, Bui Q, et al. Examining common mental health disorders in people living with HIV on methadone maintenance therapy in Hanoi, Vietnam. *Harm reduction journal.* 2021;18(1):45.

229. McGowan JA, Sherr L, Rodger AJ, et al. Age, time living with diagnosed HIV infection, and self-rated health. *HIV medicine.* 2017;18(2):89-103.

230. Duko B, Ayalew M, Ayano G. The prevalence of alcohol use disorders among people living with HIV/AIDS: a systematic review and meta-analysis. *Substance abuse treatment, prevention, and policy.* 2019;14(1):52.

231. Camara A, Sow MS, Touré A, et al. Anxiety and depression among HIV patients of the infectious disease department of Conakry University Hospital in 2018. *Epidemiol Infect.* 2020;148:e8-e8.

232. Bilal U, McCaul ME, Crane HM, et al. Predictors of Longitudinal Trajectories of Alcohol Consumption in People with HIV. *Alcoholism, clinical and experimental research.* 2018;42(3):561-570.

233. Aljassem K, Raboud JM, Hart TA, et al. Gender Differences in Severity and Correlates of Depression Symptoms in People Living with HIV in Ontario, Canada. *Journal of the International Association of Providers of AIDS Care.* 2016;15(1):23-35.

234. Shi D, Lee T, Maydeu-Olivares A. Understanding the Model Size Effect on SEM Fit Indices. *Educational and Psychological Measurement.* 2018;79(2):310-334.

235. Bentler PM, Bonett DG. Significance tests and goodness of fit in the analysis of covariance structures. *Psychological bulletin.* 1980;88(3):588-606.

236. Kass RE, Raftery AE. Bayes Factors. *Journal of the American Statistical Association.* 1995;90(430):773-795.

237. Bollen KA. *Structural Equations with Latent Variables.* New York: John Wiley and Sons, Inc.; 1989.

238. Enders CK, Bandalos DL. The Relative Performance of Full Information Maximum Likelihood Estimation for Missing Data in Structural Equation Models. *Structural Equation Modeling: A Multidisciplinary Journal.* 2001;8(3):430-457.

239. Lofgren SM, Bond DJ, Nakasujja N, Boulware DR. Burden of Depression in Outpatient HIV-Infected adults in Sub-Saharan Africa; Systematic Review and Meta-analysis. *AIDS and behavior.* 2020;24(6):1752-1764.

240. Rezaei S, Ahmadi S, Rahmati J, et al. Global prevalence of depression in HIV/AIDS: a systematic review and meta-analysis. *BMJ Supportive & Palliative Care.* 2019;9(4):404.

241. Karen Glanz MDS. Stress, coping and health behavior. In: Karen Glanz BKR, K. Viswanath, ed. San Francisco, CA: Jossey-Bass; 2008.

242. Abas M, O'Cleirigh C. Global mental health and the ambition to end AIDS by 2030. *The Lancet Psychiatry.* 2018;5(11):867-869.

243. So-Armah K, Gupta SK, Kundu S, et al. Depression and all-cause mortality risk in HIV-infected and HIV-uninfected US veterans: a cohort study. *HIV medicine.* 2019;20(5):317-329.

244. Yousuf A, Mohd Arifin SR, Musa R, Md Isa ML. Depression and HIV Disease Progression: A Mini-Review. *Clinical practice and epidemiology in mental health : CP & EMH.* 2019;15:153-159.

245. Lancaster KE, Hetrick A, Sripaipan T, et al. Alcohol abstinence stigma and alcohol use among HIV patients in Thai Nguyen, Vietnam. *PloS one.* 2020;15(9):e0239330-e0239330.

246. Conigliaro J, Gordon AJ, McGinnis KA, Rabeneck L, Justice AC. How harmful is hazardous alcohol use and abuse in HIV infection: do health care providers know who is at risk? *Journal of acquired immune deficiency syndromes (1999).* 2003;33(4):521-525.

247. Justice AC, Lasky E, McGinnis KA, et al. Medical disease and alcohol use among veterans with human immunodeficiency infection: A comparison of disease measurement strategies. *Medical care.* 2006;44(8 Suppl 2):S52-60.

248. King C, Giang LM, Bart G, Kunkel L, Korthuis PT. HIV care continuum characteristics among people with opioid use disorder and HIV in Vietnam: baseline results from the BRAVO study. *BMC public health.* 2020;20(1):421.

249. Kresina TF, Flexner CW, Sinclair J, et al. Alcohol use and HIV pharmacotherapy. *AIDS research and human retroviruses.* 2002;18(11):757-770.

250. Chichetto NE, Kundu S, Freiberg MS, et al. Association of Syndemic Unhealthy Alcohol Use, Cigarette Use, and Depression With All-Cause Mortality Among Adults Living With and Without HIV Infection: Veterans Aging Cohort Study. *Open Forum Infectious Diseases.* 2019;6(6).

251. Go VF, Hutton HE, Ha TV, et al. Effect of 2 Integrated Interventions on Alcohol Abstinence and Viral Suppression Among Vietnamese Adults With Hazardous Alcohol Use and HIV: A Randomized Clinical Trial. *JAMA Netw Open.* 2020;3(9):e2017115.

252. Giang KB, Spak F, Dzung TV, Allebeck P. The use of audit to assess level of alcohol problems in rural Vietnam. *Alcohol and alcoholism (Oxford, Oxfordshire).* 2005;40(6):578-583.

253. Tran BX, Nguyen HLT, Le QNH, et al. Alcohol and tobacco use among methadone maintenance patients in Vietnamese rural mountainside areas. *Addictive behaviors reports.* 2018;7:19-25.

254. Tran BX, Nguyen LT, Do CD, Nguyen QL, Maher RM. Associations between alcohol use disorders and adherence to antiretroviral treatment and quality of life amongst people living with HIV/AIDS. *BMC public health.* 2014;14:27.

255. Vu HM, Tran TT, Vu GT, et al. Alcohol Use Disorder among Patients Suffered from Road Collisions in a Vietnamese Delta Province. *International journal of environmental research and public health.* 2019;16(13):2423.

256. Löwe B, Decker O, Müller S, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Medical care.* 2008;46(3):266-274.

257. Nguyen TQ, Bandeen-Roche K, Bass JK, German D, Nguyen NTT, Knowlton AR. A tool for sexual minority mental health research: The Patient Health Questionnaire (PHQ-9) as a depressive symptom severity measure for sexual minority women in Viet Nam. *J Gay Lesbian Ment Health.* 2016;20(2):173-191.

258. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine.* 2001;16(9):606-613.

259. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. *Archives of internal medicine.* 2006;166(10):1092-1097.

260. Round JM, Lee C, Hanlon JG, Hyshka E, Dyck JRB, Eurich DT. Changes in patient health questionnaire (PHQ-9) scores in adults with medical authorization for cannabis. *BMC public health.* 2020;20(1):987-987.

261. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Medical care.* 2004;42(12):1194-1201.

262. Francis JM, Helander A, Kapiga SH, Weiss HA, Grosskurth H. Validation of the MINI (DSM IV) Tool for the Assessment of Alcohol Dependence among Young People in Northern Tanzania Using the Alcohol Biomarker Phosphatidylethanol (PEth). *International journal of environmental research and public health.* 2015;12(11):14021-14033.

263. Lam WY, Fresco P. Medication Adherence Measures: An Overview. *BioMed research international.* 2015;2015:217047.

264. Asangbeh SL, Sobngwi JL, Ekali GL, Eyoum C, Msellati P. Predictors of depression among patients on art in a rural health district in North West Cameroon. *AIDS Care.* 2016;28(2):205-208.

265. Familiar I, Murray S, Ruisenor-Escudero H, et al. Socio-demographic correlates of depression and anxiety among female caregivers living with HIV in rural Uganda. *AIDS Care.* 2016;28(12):1541-1545.

266. Lu B, Preisser JS, Qaqish BF, Suchindran C, Bangdiwala SI, Wolfson M. A comparison of two bias-corrected covariance estimators for generalized estimating equations. *Biometrics.* 2007;63(3):935-941.

267. Onyebuchi-Iwudibia O, Brown A. HIV and depression in Eastern Nigeria: the role of HIV-related stigma. *AIDS Care.* 2014;26(5):653-657.

268. Slot M, Sodemann M, Gabel C, Holmskov J, Laursen T, Rodkjaer L. Factors associated with risk of depression and relevant predictors of screening for depression in clinical practice: a cross-sectional study among HIV-infected individuals in Denmark. *HIV medicine.* 2015;16(7):393-402.

269. Tanner Z, Lachowsky N, Ding E, et al. Predictors of viral suppression and rebound among HIV-positive men who have sex with men in a large multi-site Canadian cohort. *BMC infectious diseases.* 2016;16(1):590.

270. Wouters E, Masquillier C, le Roux Booysen F. The Importance of the Family: A Longitudinal Study of the Predictors of Depression in HIV Patients in South Africa. *AIDS and behavior.* 2016;20(8):1591-1602.

271. Sherbourne CD, Stewart AL. The MOS social support survey. *Social science & medicine (1982).* 1991;32(6):705-714.

272. Miller WC, Hoffman IF, Hanscom BS, et al. A scalable, integrated intervention to engage people who inject drugs in HIV care and medication-assisted treatment (HPTN 074): a randomised, controlled phase 3 feasibility and efficacy study. *Lancet (London, England).* 2018;392(10149):747-759.

273. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol.* 2014;67(3):267-277.

274. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. *BMC medical research methodology.* 2007;7:30-30.

275. Vitasari P, Wahab MNA, Herawan T, Sinnadurai SK, Othman A, Awang MG. Assessing of Physiological Arousal and Cognitive Anxiety toward Academic Performance: The Application of Catastrophe Model. *Procedia - Social and Behavioral Sciences.* 2011;30:615-619.

276. Arent SM, Landers DM. Arousal, anxiety, and performance: a reexamination of the Inverted-U hypothesis. *Research quarterly for exercise and sport.* 2003;74(4):436-444.

277. Quan VM, Minh NL, Ha TV, et al. Mortality and HIV transmission among male Vietnamese injection drug users. *Addiction (Abingdon, England).* 2011;106(3):583-589.

278. Hayes-Larson E, Grau LE, Khoshnood K, Barbour R, Khuat OTH, Heimer R. Drug users in Hanoi, Vietnam: factors associated with membership in community-based drug user groups. *Harm reduction journal.* 2013;10(1):33.

279. Seffren V, Familiar I, Murray SM, et al. Association between coping strategies, social support, and depression and anxiety symptoms among rural Ugandan women living with HIV/AIDS. *AIDS Care.* 2018;30(7):888-895.

280. Rychtarik RG, McGillicuddy NB. Coping skills training and 12-step facilitation for women whose partner has alcoholism: effects on depression, the partner's drinking, and partner physical violence. *Journal of consulting and clinical psychology.* 2005;73(2):249-261.

281. Matsumoto S, Yamaoka K, Takahashi K, et al. Social Support as a Key Protective Factor against Depression in HIV-Infected Patients: Report from large HIV clinics in Hanoi, Vietnam. *Sci Rep.* 2017;7(1):15489-15489.

282. Drapkin ML, Eddie D, Buffington AJ, McCrady BS. Alcohol-Specific Coping Styles of Adult Children of Individuals with Alcohol Use Disorders and Associations with Psychosocial Functioning. *Alcohol and Alcoholism.* 2015;50(4):463-469.

283. Besthorn F, Kalomo EN, Lightfoot E, Liao M. The relationship between social support and anxiety amongst children living with HIV in rural northern Namibia. *African journal of AIDS research : AJAR.* 2018;17(4):293-300.

284. Green K, Tuan T, Hoang TV, Thi Trang NN, Thanh Ha NT, Hung ND. Integrating Palliative Care Into HIV Outpatient Clinical Settings: Preliminary Findings From an Intervention Study in Vietnam. *Journal of Pain and Symptom Management.* 2010;40(1):31-34.

285. Smith JP, Randall CL. Anxiety and alcohol use disorders: comorbidity and treatment considerations. *Alcohol Res.* 2012;34(4):414-431.

286. Sullivan LE, Saitz R, Cheng DM, Libman H, Nunes D, Samet JH. The impact of alcohol use on depressive symptoms in human immunodeficiency virus-infected patients. *Addiction (Abingdon, England).* 2008;103(9):1461-1467.

287. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British journal of addiction.* 1989;84(11):1353-1357.

288. Wagner GJ, Ghosh-Dastidar B, Garnett J, Kityo C, Mugyenyi P. Impact of HIV antiretroviral therapy on depression and mental health among clients with HIV in Uganda. *Psychosomatic medicine.* 2012;74(9):883-890.

289. US PEPFAR. *Vietnam Country Operational Plan (COP/ROP) 2020: Strategic Direction Summary* 2020.

290. Van Tam V, Cuong DD, Alfven T, et al. HIV sero-discordance among married HIV patients initiating anti-retroviral therapy in northern Vietnam. *AIDS Res Ther.* 2016;13:39-39.

291. Than PQT, Tran BX, Nguyen CT, et al. Stigma against patients with HIV/AIDS in the rapid expansion of antiretroviral treatment in large drug injection-driven HIV epidemics of Vietnam. *Harm reduction journal.* 2019;16(1):6.

292. Nguyen Bich D, Korthuis PT, Nguyen Thu T, Van Dinh H, Le Minh G. HIV Patients' Preference for Integrated Models of Addiction and HIV Treatment in Vietnam. *Journal of substance abuse treatment.* 2016;69:57-63.

293. Miller WR. *Project COMBINE: Combined Behavioral Intervention (CBI) - Therapist Manual.* 2002.

294. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined Pharmacotherapies and Behavioral Interventions for Alcohol DependenceThe COMBINE Study: A Randomized Controlled Trial. *Jama.* 2006;295(17):2003-2017.

295. Kuria MW, Ndetei DM, Obot IS, et al. The Association between Alcohol Dependence and Depression before and after Treatment for Alcohol Dependence. *ISRN Psychiatry.* 2012;2012:482802-482802.

296. Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: a systematic review. *The American journal of medicine.* 2005;118(4):330-341.

297. Kushner MG, Abrams K, Thuras P, Hanson KL, Brekke M, Sletten S. Follow-up study of anxiety disorder and alcohol dependence in comorbid alcoholism treatment patients. *Alcoholism, clinical and experimental research.* 2005;29(8):1432-1443.

298. Torvik FA, Rosenström TH, Gustavson K, et al. Explaining the association between anxiety disorders and alcohol use disorder: A twin study. *Depression and Anxiety.* 2019;36(6):522-532.

299. Brown SA, Irwin M, Schuckit MA. Changes in anxiety among abstinent male alcoholics. *Journal of studies on alcohol.* 1991;52(1):55-61.

300. Abrams K, Kushner M, Medina KL, Voight A. The pharmacologic and expectancy effects of alcohol on social anxiety in individuals with social phobia. *Drug and alcohol dependence.* 2001;64(2):219-231.

301. Schuckit MA, Hesselbrock V. Alcohol dependence and anxiety disorders: what is the relationship? *The American journal of psychiatry.* 1994;151(12):1723-1734.

302. Swendsen JD, Merikangas KR. The comorbidity of depression and substance use disorders. *Clinical psychology review.* 2000;20(2):173-189.

303. DeVido JJ, Weiss RD. Treatment of the depressed alcoholic patient. *Current psychiatry reports.* 2012;14(6):610-618.

304. Satre DD, Leibowitz A, Sterling SA, Lu Y, Travis A, Weisner C. A randomized clinical trial of Motivational Interviewing to reduce alcohol and drug use among patients with depression. *Journal of consulting and clinical psychology.* 2016;84(7):571-579.

305. Baker AL, Thornton LK, Hiles S, Hides L, Lubman DI. Psychological interventions for alcohol misuse among people with co-occurring depression or anxiety disorders: a systematic review. *J Affect Disord.* 2012;139(3):217-229.

306. Baker AL, Kavanagh DJ, Kay-Lambkin FJ, et al. Randomized controlled trial of cognitive-behavioural therapy for coexisting depression and alcohol problems: short-term outcome. *Addiction (Abingdon, England).* 2010;105(1):87-99.

307. Kay-Lambkin FJ, Baker AL, Lewin TJ, Carr VJ. Computer-based psychological treatment for comorbid depression and problematic alcohol and/or cannabis use: a randomized controlled trial of clinical efficacy. *Addiction (Abingdon, England).* 2009;104(3):378-388.

308. Kenny DA, Judd CM. Power Anomalies in Testing Mediation. *Psychological Science.* 2013;25(2):334-339.

309. Zhao X, Lynch JG, Jr., Chen Q. Reconsidering Baron and Kenny: Myths and Truths about Mediation Analysis. *Journal of Consumer Research.* 2010;37(2):197-206.

310. Rucker DD, Preacher KJ, Tormala ZL, Petty RE. Mediation Analysis in Social Psychology: Current Practices and New Recommendations. *Social and Personality Psychology Compass.* 2011;5(6):359-371.

311. Hayes AF. Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium. *Communication Monographs.* 2009;76(4):408-420.

312. Boden JM, Fergusson DM. Alcohol and depression. *Addiction (Abingdon, England).* 2011;106(5):906-914.

313. Foulds JA, Douglas Sellman J, Adamson SJ, Boden JM, Mulder RT, Joyce PR. Depression outcome in alcohol dependent patients: An evaluation of the role of independent and substance-induced depression and other predictors. *J Affect Disord.* 2015;174:503-510.

314. Nguyen MX, Go VF, Bui QX, Gaynes BN, Pence BW. Perceived need, barriers to and facilitators of mental health care among HIV-infected PWID in Hanoi, Vietnam: a qualitative study. *Harm reduction journal.* 2019;16(1):74.

315. Ezeanolue EE, Iheanacho T, Adedeji IA, et al. Opportunities and challenges to integrating mental health into HIV programs in a low- and middle-income country: insights from the Nigeria implementation science Alliance. *BMC Health Serv Res.* 2020;20(1):904.

316. Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health problems: Current status and future directions. *Journal of consulting and clinical psychology.* 2020;88(3):179-195.

317. Choi JY. Mental health of HIV-infected patients: A severe, but Overlooked Problem. *Infect Chemother.* 2013;45(2):239-240.

318. Trang K, Ly AT, Lam LX, et al. Mental health in HIV prevention and care: A qualitative study of challenges and facilitators to integration in Vietnam. *Social science & medicine (1982).* 2021;279:113978.

319. World Health Organization. *Mental Health Atlas 2014 Country Profile.* 2014.

320. Vuong DA, Van Ginneken E, Morris J, Ha ST, Busse R. Mental health in Vietnam: Burden of disease and availability of services. *Asian journal of psychiatry.* 2011;4(1):65-70.

321. Kulisewa K, Stockton MA, Hosseinipour MC, et al. The Role of Depression Screening and Treatment in Achieving the UNAIDS 90-90-90 Goals in Sub-Saharan Africa. *AIDS and behavior.* 2019;23(Suppl 2):153-161.

322. Wagner GJ, Ngo V, Goutam P, Glick P, Musisi S, Akena D. A Structured Protocol Model of Depression Care versus Clinical Acumen: A Cluster Randomized Trial of the Effects on Depression Screening, Diagnostic Evaluation, and Treatment Uptake in Ugandan HIV Clinics. *PloS one.* 2016;11(5):e0153132-e0153132.

323. Dorsey S, Gray CL, Wasonga AI, et al. Advancing successful implementation of task-shifted mental health care in low-resource settings (BASIC): protocol for a stepped wedge cluster randomized trial. *BMC psychiatry.* 2020;20(1):10-10.

324. Chibanda D, Weiss HA, Verhey R, et al. Effect of a Primary Care–Based Psychological Intervention on Symptoms of Common Mental Disorders in Zimbabwe: A Randomized Clinical Trial. *Jama.* 2016;316(24):2618-2626.

325. Adams JL, Almond ML, Ringo EJ, Shangali WH, Sikkema KJ. Feasibility of nurse-led antidepressant medication management of depression in an HIV clinic in Tanzania. *International journal of psychiatry in medicine.* 2012;43(2):105-117.

326. World Health Organization. Task shifting: Global Recommendations and Guidelines. In. Geneva, Switzerland2008.

327. Shirley DK, Kaner RJ, Glesby MJ. Effects of Smoking on Non-AIDS-Related Morbidity in HIV-Infected Patients. *Clinical Infectious Diseases.* 2013;57(2):275-282.

328. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. *Annals of family medicine.* 2009;7(4):357-363.

329. Lorenc A, Ananthavarathan P, Lorigan J, Jowata M, Brook G, Banarsee R. The prevalence of comorbidities among people living with HIV in Brent: a diverse London Borough. *London J Prim Care (Abingdon).* 2014;6(4):84-90.

330. Winston A, De Francesco D, Post F, et al. Comorbidity indices in people with HIV and considerations for coronavirus disease 2019 outcomes. *AIDS (London, England).* 2020;34(12):1795-1800.

331. Nguyen MX, Dowdy D, Latkin CA, et al. Social support modifies the association between hazardous drinking and depression symptoms among ART clients in Vietnam. *Drug and alcohol dependence.* 2020:108249.