

IMPACT OF DEPRESSION AND ANXIETY ON ANTIRETROVIRAL THERAPY  
INITIATION AND ADHERENCE AMONG NEWLY DIAGNOSED HIV-INFECTED  
MEN WHO HAVE SEX WITH MEN IN CHINA

By

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## DEDICATION

To my dear family, my mother Yun, and my husband Hao,  
For their infinitely love and support.

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## TABLE OF CONTENTS

	Page
DEDICATION .....	ii
ACKNOWLEDGEMENTS .....	iii
LIST OF TABLES .....	viii
LIST OF FIGURES .....	x
LIST OF ABBREVIATIONS.....	xi
Chapter	
I. INTRODUCTION.....	1
The global HIV epidemic among men who have sex with men .....	1
HIV surveillance among Chinese MSM .....	3
Prevention with positives .....	4
Depression and anxiety disorders among MSM .....	9
The impact of depression on “prevention with positives” .....	10
The impact of anxiety on “prevention with positives” .....	11
II. SPECIFIC AIMS AND INNOVATION.....	13
Specific aims .....	13
Innovations.....	17
III. OVERALL STUDY DESCRIPTION.....	20
Study design.....	20
Study population .....	21
Recruitment .....	22
Intervention .....	24
Data collection .....	25
Laboratory testing.....	27
IV. ASSOCIATION BETWEEN DEPRESSION AND INITIATION OF ANTIRETROVIRAL THERAPY AMONG HIV-INFECTED PEOPLE: A META- ANALYSIS.....	29
Abstract .....	29

Introduction .....	30
Methods .....	32
Results .....	36
Discussion .....	44
V. IMPACT OF DEPRESSION AND ANXIETY ON INITIATION OF ANTIRETROVIRAL THERAPY AMONG CHINESE MEN WHO HAVE SEX WITH MEN WITH NEWLY DIAGNOSED HIV INIFECTIONS.....	48
Abstract .....	48
Introduction .....	49
Methods.....	52
Results .....	55
Discussion .....	66
VI. EFFECTS OF DEPRESSION AND ANXIETY ON ADHERENCE TO ANTIRETROVIRAL THERAPY AMONG NEWLY DIAGNOSED HIV-INFECTED CHINESE MEN WHO HAVE SEX WITH MEN .....	71
Abstract .....	71
Introduction .....	72
Methods.....	74
Results .....	77
Discussion .....	82
VII. PEER COUNSELING FOR DEPRESSION AND ANXIETY AMONG NEWLY DIAGNOSED HIV-INFECTED MEN WHO HAVE SEX WITH MEN, IN CHINA: A RANDOMIZED CLINICAL TRIAL .....	85
Abstract .....	85
Introduction .....	86
Methods.....	88
Results .....	91
Discussion .....	96
VIII. SYNOPSIS.....	99
REFERENCES .....	105

## LIST OF TABLES

Table	Page
1. Frequency of repeated measurements of covariates during 12 months follow-up .....	25
2. List of eligible studies for the meta-analysis of depression on ART initiation among HIV-infected people .....	40
3. Results of pooled odds ratios for the association between depression and ART initiation from subgroup analyses .....	42
4. Results of pooled estimation in the sensitivity analyses .....	42
5. Demographic and behavioral characteristics among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections by initiation of antiretroviral therapy (ART) .....	57
6. Frequency of 9 combinations of depression and anxiety categories among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections .....	61
7. Association between baseline depression/anxiety scores and antiretroviral therapy (ART) initiation among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections .....	62
8. Association between categories of depression and anxiety and antiretroviral therapy (ART) among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections .....	64
9. Demographics, behaviors, and health status among 228 Chinese men who have sex with men (MSM) who initiated antiretroviral therapy (ART) .....	80
10. Association between depression and anxiety and adherence to antiretroviral therapy among Chinese men who have sex with men (MSM) who initiated ART .....	81
11. Categorical depression and anxiety among 367 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections over 12 months follow-up .....	94



12. The effect of peer counseling on depression and anxiety among 367 newly diagnosed HIV-infected men who have sex with men (MSM) in Beijing .....	96
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## LIST OF FIGURES

Figure	Page
1. Available HIV testing venues for Chinese MSM .....	5
2. The overall design of our project .....	21
3. The flow chart of literature selection .....	37
4. Forest plot of depression on ART initiation among HIV-infected people .....	41
5. Funnel plot for publication bias .....	44
6. Associations between baseline depression/anxiety scores and hazard of antiretroviral therapy (ART) initiation (log function) among 364 Chinese men who have sex with men (MSM) .....	63
7. Cumulative antiretroviral therapy (ART) initiation of depression/anxiety among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections .....	65
8. Box plot of the depression and/or anxiety score among 367 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections over 12 months follow- up .....	93

## LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
CBOs	Community-based organizations
China CDC	Chinese Center for Disease Control and Prevention
DAG	Directed Acyclic Graph
ELISA	Enzyme-linked immunosorbent assays
GEE	Generalized estimation equation
HADS	Hospital anxiety and depression scale
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IDU	Intravenous drug use
LMIC	Low and/or Middle income countries
LRT	Likelihood ratio test
MSM	Men Who Have Sex with Men
NARL	National AIDS reference laboratory
OR	Odds Ratio
PCs	Peer counselors
PLHIV	People living with HIV
PrEP	Pre-exposure prophylaxis
PT	Proficiency test

PWID	People who inject drugs
QA	Quality assurance
RCT	Randomized clinical trial
RNA	Ribonucleic acid
SMS-I	Short Message Service-I
SMS-II	Short Message Service-II
STDs	Sexually transmitted diseases
TLC	Testing and Linkage-to-Care
U.S. CDC	U.S. Centers for Disease Control and Prevention
UAI	Unprotected anal intercourse
VCT	Voluntary counseling and testing
VIGH	Vanderbilt Institute for Global Health

## CHAPTER I

### INTRODUCTION

#### **The global HIV epidemic among men who have sex with men**

Homosexuality can be traced back to the ancient time, but it was not seen as a legitimate topic for public attention until the 1970s. Since the first AIDS case was found among men who have sex with men (MSM) in 1981, MSM has disproportionately represented in existing and new HIV/AIDS cases in high-income countries, for example, 64% of newly diagnosed cases in adult male in the U.S. were among MSM in 2012 (Centers for Disease Control Prevention, 2015). In recent years, MSM have also become the highest risk group for HIV infection in some low and middle-income countries (LMIC) (Adam et al., 2009; Baral, Sifakis, Cleghorn, & Beyrer, 2007; C. Caceres, Konda, Pecheny, Chatterjee, & Lyerla, 2006; C. F. Caceres, Konda, Segura, & Lyerla, 2008; Ma et al., 2007). Hence, the HIV epidemic among MSM is now recognized as a global issue (Beyrer et al., 2012). According to Global AIDS report in 2013, HIV prevalence among MSM varied in different regions, with the highest prevalence in Western and central Africa (19%), followed by Eastern and Southern Africa (15%), Latin America (12%), Asia and Pacific (11%), Europe and North America (8%), and the Caribbean (7%) ("2013 UNAIDS Report on the global AIDS epidemic," 2013). UNAIDS reported there were 2.3 (1.9-2.7) million new HIV infections in 2012. In Asia and the Pacific, the estimated

number of new HIV infections was 0.35 million in 2012, and the proportion of new HIV infections from MSM ranged from 7% to 80% across countries (Dabaghzadeh, Khalili, Ghaeli, & Alimadadi, 2013). Based on the national sentinel surveillance data, HIV prevalence among Chinese MSM has risen from 0.9% in 2003 to 7.7% in 2014 (Joint United Nations Programme on HIV/AIDS, 2015; Wang et al., 2012). More than 20% of new HIV cases in China were from MSM since 2013 (Joint United Nations Programme on HIV/AIDS, 2015). In recent years, the Chinese government has allocated more resources for preventing and controlling the HIV epidemic in this population (Lau, Lin, Hao, Wu, & Gu, 2011).

MSM are a hidden population, as they face the dual stigma of HIV infection and homosexuality (Bird & Voisin, 2011). Hence, only a small proportion of MSM may disclose their sexual identity (Fan et al., 2012; Wei, Lim, Guadamuz, & Koe, 2012). The Chinese Ministry of Health reported that China had at least 10 million active MSM in 2004; other research has suggested that the estimated number of MSM could be as high as 24 million (Zou, Hu, Xin, & Beck, 2012). Mathematic model indicated that the incidence is likely to continue to increase by 2020 even with expanded coverage of prevention interventions (Lou et al., 2014). However, the concept of effective intervention is complex for MSM, since many prevention strategies have not worked well. Experts believe that MSM will be one of the highest risk groups for HIV acquisition through 2025 in China. Meanwhile, HIV prevalence has decreased in people who inject drugs (PWID) due to effective interventions including needle exchanges and methadone substitution therapy (Jarlais, 2013; Wang et al., 2011; L. Zhang et al., 2013). Therefore,

more efforts and resources should be allocated to HIV prevention interventions among Chinese MSM.

### **HIV surveillance among Chinese MSM**

China established first national HIV sentinel surveillance sites among PWID, female sex workers, STD clinic attendees and long-distance truck drivers in 1995, and expanded the sites for MSM until 2002 (Sun et al., 2007). The 0.9% HIV prevalence among Chinese MSM documented in 2003 in a limited region, and the estimated 10 million or more MSM in China made HIV infections a serious public concern in this key population (Chen et al., 2013; Ning et al., 2007). HIV sentinel surveillance is an active system to monitor the HIV epidemic, and each year two rounds of surveillance are enacted in high-risk populations. Each sentinel surveillance site is required to enroll 200 MSM in an anonymous way. HIV screening test results are reported semiannually. As of 2011, there are 108 sentinel sites among MSM in 31 provinces in mainland China except Xizang (or Tibet) (Wang et al., 2012).

Complementing active surveillance is a passive HIV monitoring system, comprised of clinic/hospital-based HIV testing and voluntarily counseling and testing (VCT). These facilities offer HIV testing and counseling, while VCT sites sponsored by the Chinese government provide additional free services. Hospital-based and government-sponsored testing sites are widely available at the county-level, and the government does their best effort to make sure that people have access to HIV testing, especially for high-risk men and subgroups. However, 50% to 80% of MSM report HIV

testing barriers in public testing sites (Li et al., 2012; Song et al., 2011). The top five HIV testing barriers include a fear of a HIV positive result, unwillingness to visit a public testing site, a fear of discrimination, not knowing where to go for HIV testing, and not perceiving any risk for HIV (Li et al., 2012). To fill in the testing gap, community-based organizations (CBOs) offer HIV rapid testing at MSM gathering sites, such as gay bars and bathhouses. Another testing mode is home-based HIV self-testing, MSM can purchase HIV testing kits online, typically then mailed to their homes within three days (J. Tao et al., 2014). MSM can perform the test and read the test result with guidance from the on-line video instruction. A hot line is also available to provide free counseling; referrals for confirmatory testing and HIV care are also offered during counseling. The combined surveillance system in China is expected to comprehensively monitor the HIV epidemic among MSM, but there remain gaps.

### **Prevention with Positives**

HIV prevention and intervention among MSM is a great challenge, and the control of the HIV epidemic among MSM may take decades (HIV/AIDS, 2010). HIV prevention and intervention mainly have two components: the prevention of HIV acquisition in HIV uninfected men, and the avoidance of transmission from HIV infected men. Most efforts have been placed on preventing HIV negative people from acquiring infections. “Prevention with positives”-focusing on reducing risk behaviors among people living with HIV (PLHIV) was not recommended until 2003 by the U.S. CDC. This approach can be cost-effective, as it only needs to target HIV infected MSM



comprising 10 percent of all MSM, rather than the remaining 90% HIV seronegative MSM (HIV/AIDS, 2010). HIV testing and linkage-to-care model is the core strategy for the Prevention with positives underscoring the need to reduce their transmission via risk reduction and ART (“treatment as prevention”) (Vermund & Hayes, 2013).

### HIV testing and linkage-to-care

The HIV testing and linkage-to-care (TLC) model includes HIV testing, counseling, and the continuum of HIV care (retention, initiation and adherence to ART). Full engagement in the TLC can be expected to improve quality of life of PLHIV and to reduce HIV secondary transmission. HIV testing is essential to screen the HIV negative population, diagnose new cases, and offer ART treatment when indicated. HIV testing is a voluntary behavior, and it is only mandatory in China for patients who receive invasive procedures or surgery.

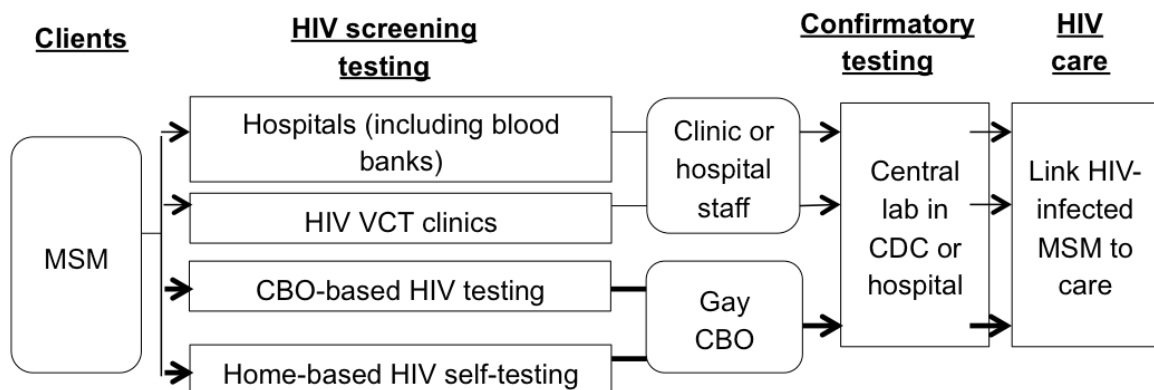


Figure 1 Available HIV testing venues for Chinese MSM (J. Tao et al., 2014)

Currently, four venues are available for Chinese MSM to take a test (Figure 1). Hospital based HIV testing is usually provider-initiated, and it is not free of charge. MSM can get free testing and counseling at VCT sites, which are sponsored by government. CBO-based and home-based HIV testing are supplementary venues to public testing sites. Many MSM are reluctant to go to the public testing sites due to fears of losing privacy or confidentiality, and may prefer the CBO or home-based options. Pre and post-test counseling are provided by staff or peers with an expectation of having an impact on reducing risky behaviors (Jackson et al., 2013). MSM who test seropositive are referred for HIV confirmatory diagnosis. CD4+ T cell counts (CD4 count) are offered for PLHIV for free every six months; health care workers provide advice and suggestions for ART initiation according to individual's disease status and the national ART treatment guideline. Recently, a policy that individuals are encouraged to initiate treatment as early as possible has been adopted. Currently, the Chinese government provides free drugs for PLHIV regardless of CD4 count. Early treatment can serve as the secondary prevention, as it can reduce secondary transmission by lowering viral load (M. S. Cohen, McCauley, & Gamble, 2012; Marchetti et al., 2012; Padian et al., 2011; Smith, Powers, Kashuba, & Cohen, 2011). Viral load testing is used to indicate viral suppression and treatment adherence. However, viral load testing costs 150 U.S. dollar per test, and it is not covered by the government currently. But, it is highly recommended for PLHIV on ART. HIV testing, counseling, CD4 count monitoring, and ART initiation and adherence are the main components of HIV testing linkage-to-care model.

Although the above HIV testing and care cascade holds promise for both treatment and prevention, the real situation in China is not sanguine. Survey evidence has

shown that 28%-57% of Chinese MSM had never been tested (Choi, Lui, Guo, Han, & Mandel, 2006; Li et al., 2012; Song et al., 2011; J. Tao et al., 2014). Untested MSM were more likely to be younger, less educated, and reporting multiple sexual partners with a higher risk of HIV acquisition (Chow et al., 2013; Fernandez-Davila et al., 2013).

Modeling has estimated that 87% of HIV infected MSM did not know their seropositivity (Chow, Wilson, & Zhang, 2010). In contrast, the percentage of never tested MSM ranges from 20% to 28% in European countries and the U.S.(Carvalho et al., 2013; Fernandez-Davila et al., 2013; Knussen, Flowers, & McDaid, 2014; Mitchell & Horvath, 2013).

In one-study from 15 cities supported by the China-Gates foundation, 21% of Chinese MSM with a positive screening result did not go for confirmatory test, and 34% of diagnosed cases were lost before linkage to care (D. Zhang et al., 2014). The proportions of MSM retained in care, initiated ART, adhered to treatment, and virally suppressed are still unknown. In comparison, among diagnosed HIV-infected MSM in the U.S., 50.9% were retained in care, 49.5% took up ART, and 42% had successful viral suppression (Singh et al., 2014). Research on HIV testing and the continuum of HIV care are required to fill in the gap of health service knowledge, and efforts should be paid to improve the effectiveness and efficacy of this continuum of care.

#### Alternative and supplementary HIV prevention and intervention methods

Although the HIV testing and care cascade is the cornerstone of HIV control and prevention, alternative and supplementary prevention and intervention strategies are indispensable. Education on HIV transmission and prevention can have an impact on

improvement on risk perception and reduction in risky behaviors, and it might also motivate Chinese MSM to take a test for HIV. In China, HIV education messages are conveyed by bulletin boards at schools and communities, pamphlets, TV shows, newspapers, and websites (French, Bonell, Wellings, & Weatherburn, 2014). Although MSM represent a hidden population, the HIV/AIDS knowledge is expected to reach a majority of Chinese MSM. Two studies in 2009 and 2013 have shown that 78.1% to 98.9% of Chinese MSM know about HIV transmission routes (Liu, Qu, Ezeakile, Zhang, & Liang, 2013; Yingjun Zheng et al., 2009). Condom use is the most effective way to protect MSM from HIV acquisition. Consistent and correct condom use can reduce the risk of HIV acquisition per contact with HIV positive or unknown serostatus male sexual partners. Vittinghoff et al. estimated that the per contact risk for HIV acquisition among MSM with consistent condom use went down to 0.18 percent (95% CI: 0.10,0.28), compared to 0.82 percent and 0.27 percent among MSM who had unprotected anal intercourse (UAI) with HIV positive and unknown sero-status male sexual partners from three large cohort in the U.S. in 1999, respectively (Vittinghoff et al., 1999). Preexposure prophylaxis (PrEP) is an alternative prevention strategy for MSM. PrEP has been associated with a reduced risk of HIV acquisition among high-risk populations in a meta-analysis (Okwundu, Uthman, & Okoromah, 2012). Although PrEP has not been widely used in China, almost 70% of Chinese MSM stated that they were willing to take PrEP (Y. Zhang et al., 2013; Zhou et al., 2012). Hence, it could be a promising prevention for Chinese MSM. Although the protective effect of male circumcision for HIV acquisition has been proved in three RCTs among heterosexual men in Africa (Auvert et al., 2005; Bailey et al., 2007; Gray et al., 2007), the protective effect among MSM is controversial

(Vermund & Qian, 2008). Based on biological plausibility, only men who prefer an exclusively insertive role are likely to benefit from circumcision. STD treatment, therapy for drug and alcohol abuse, and treatment of mental health disorders can also play a role in the control of HIV epidemic among Chinese MSM.

### **Depression and anxiety disorders among MSM**

Only 3% to 5% of people identify themselves as homosexual or bisexual worldwide. This minority group lives in a hostile and stressful social environment caused by stigma, prejudice, and discrimination, and they endure more negative events than the general population (Meyer, 2003). Negative events, such as stress, isolation, and hostility, are external triggers for mental illnesses. Research has shown that MSM have a doubled risk of having mental disorders, when compared to the general male population (King et al., 2008; Meyer, 2003; Meyer, Dietrich, & Schwartz, 2008). Mental health disorders may include anxiety, depression, bipolar disorder, personality disorder and psychosis. Depression and Anxiety disorders are common among MSM. The lifetime prevalence of depression among MSM in the U.S. ranged from 9.7% to 30.2%, and the lifetime prevalence of anxiety varied from 18.7% to 43.7% documented in 2007 and 2008 (Cochran, Mays, Alegria, Ortega, & Takeuchi, 2007; Meyer et al., 2008). Limited studies have focused on the mental health of Chinese MSM, and one study found that a lifetime prevalence of depression was 11.7%, and a lifetime prevalence of anxiety disorder was 18.6% among Chinese MSM in 2013 (Yu et al., 2013).

## **The impact of depression on “prevention with positives”**

Depression is a persistent mood disorder, and patients feel sad, lost, angry, frustrated and interfered in their everyday lives. The main types of depression include major depression, dysthymia, and minor depression. The components of depression are inconsistent. Depression sometimes stands for major depression, but it can also be used to indicate the sum of major depression and dysthymia. In rare cases, researchers include bipolar disorder as one of its components. In this dissertation, depression is defined to include major depression, dysthymia, and minor depression. As the scale we used to measure depression cannot differentiate the severity of depression.

Mental disorders have been confirmed to have an association with unprotected sexual intercourse, multiple sexual partners, and HIV infections across several studies (Kelly et al., 1993; Koblin et al., 2006; Meade & Sikkema, 2005; Perdue, Hagan, Thiede, & Valleroy, 2003; Salomon et al., 2009). However, Rogers *et al.* found that only mild and persistent depression were associated with increasing unprotected sexual intercourses, and major depression was related to less sexual risk taking (Rogers et al., 2003). In addition, depression also has an association with alcohol and drug abuse, that are also risk factors of HIV infections (Reisner et al., 2009). Given the high prevalence of depression among MSM, intervention and treatment on depression can contribute to the control of HIV epidemic by improving the continuum of care through “treatment as prevention”.

Depression has a negative effect on HIV testing and HIV care. Depressed individuals experience self-abasement, cognition impairment, and self-isolation. They may avoid contact with other human beings, and they are typically less likely to seek HIV

testing. A few studies have identified depression as a barrier for seeking HIV testing (Huang et al., 2012). Evidence suggests that individuals with positive screening test of depression were less likely to show up for HIV care (Bhatia, Hartman, Kallen, Graham, & Giordano, 2011; Mayston et al., 2014; Ramirez-Avila et al., 2012; Traeger, O’Cleirigh, Skeer, Mayer, & Safren, 2012). Depression plays a negative role in ART initiation and medication adherence. Non-adherence can cause drug resistance and poor prognosis for treatment (Judith A Cook et al., 2007; Goodness et al., 2014; Ramirez-Avila et al., 2012; Barbara J Turner et al., 2001; Wagner et al., 2011; Wagner, Kanouse, Koegel, & Sullivan, 2003). Furthermore, PLHIV with depression symptoms generally have a low CD4 count and a higher viral load (Jane Leserman, 2008). Depressed PLHIV are also more likely to progress to AIDS in a shorter time than those who are not depressed (Antelman et al., 2007; J. Leserman et al., 1999; Villes et al., 2007). The majority of research on depression and HIV related outcomes was conducted in North America and Africa. Therefore, it is necessary to explore the effect of depression on HIV testing and care in China, especially among MSM.

### **The impact of anxiety disorders on “prevention with positives”**

Anxiety disorders are common, and patients in particular feel anxiety about the future. The four common types of anxiety disorders include generalized anxiety disorder, a specific phobia, social anxiety disorder, and panic disorder. An individual with anxiety disorders experiences mental apprehension, physical tension, and physical symptoms. Anxiety disorders are different from ordinary anxiety, which is transient and vanishes as triggered events ended. Anxiety disorders often occur with other psychological diseases,

such as major depression and bipolar disorder. Anxiety disorders are generally neglected, in contrast to attention paid to the effect of depression on HIV care and related outcomes. However, the literature suggests that anxiety disorders may be associated with increasing risk, such as the frequency of UAI, even when controlling for depression (Hart, James, Purcell, & Farber, 2008). Anxiety disorders may have an adverse effect on HIV care acceptance and ART initiation (Lorenza Nogueira Campos, Guimarães, & Remien, 2010; Tegger et al., 2008). Studies have also suggested that anxiety disorders have an impact on ART adherence (L. N. Campos, Guimaraes, & Remien, 2010; Joshi et al., 2014; Nilsson Schonnesson, Williams, Ross, Bratt, & Keel, 2007). Such evidence is lacking among MSM, especially for newly diagnosed HIV-infected MSM. Hence, more research is needed to fill in the gap.



## CHAPTER II

### SPECIFIC AIMS AND INNOVATIONS

#### **Specific aims**

HIV prevalence among MSM is increasing worldwide since the beginning of the 21st century. In the U.S., for example, 64% of new HIV cases were from MSM population in 2012 (Centers for Disease Control Prevention, 2015). The proportion of new HIV/AIDS cases in China from MSM is also expanding (Wang et al., 2012). As the number of HIV-infected MSM in China is increasing, prevention for HIV-infected MSM is needed to improve their quality of life, and to reduce the likelihood of HIV secondary transmission. The **HIV TLC model** is the cornerstone for “prevention with positives”. However, targeted individuals must be present at each stage to access ART and care. As lost to follow-up (LTFU) can happen at each step of the continuum of care, only a small proportion of HIV-infected Chinese MSM have received ART. Mental health disorders are important risk factors for failure to engage in the HIV continuum of care. **Depression and anxiety disorders** are common among MSM, and the lifetime prevalence of depression and anxiety disorders were reported as 11.7% and 18.6% respectively, among Chinese MSM in Liaoning province in 2013 (Yu et al., 2013). Depression has been reported to have an adverse impact on safe sex (e.g. condom use), HIV testing and care, progression to AIDS and mortality (Antelman et al., 2007; Judith A Cook et al., 2004;

Mayne, Vittinghoff, Chesney, Barrett, & Coates, 1996; Rabkin, 2008; Sherr, Clucas, Harding, Sibley, & Catalan, 2011; Vyavaharkar et al., 2010). The impact of anxiety on these outcomes is not definitive. Most evidence came from studies conducted in North America and Africa (De et al., 2013; Murray et al., 2009; Peltzer, Ramlagan, Khan, & Gaede, 2011; Pence et al., 2008; Ramirez-Avila et al., 2012; Tegger et al., 2008; Traeger et al., 2012). Hence, it is necessary to explore the impact of depression and anxiety disorders on HIV/AIDS-related outcomes among Chinese MSM.

Prevention and intervention for depression and anxiety disorders can improve their quality of life, and may contribute to curbing HIV epidemic through improved adherence to steps in the continuum of care. Medication is the standard treatment for major depression, and mild depression and anxiety may be relieved by other therapies, such as social support (Woodward & Pantalone, 2012). In this project, we evaluated the effect of peer counseling bundled with short messaging service (SMS) via cell phone on the reduction of depression and anxiety among newly diagnosed HIV-infected Chinese MSM. Peer counselors provided either face-to-face or phone-call counseling, whenever needed and desired. Peer counseling and support have been demonstrated to be a successful alternative intervention to often rushed provider-offered services (Doull, O'Connor, Wells, Tugwell, & Welch, 2004; A Molassiotis et al., 2002; Simoni, Pantalone, Plummer, & Huang, 2007). Hence, I hypothesize that study participants with peer counseling have lower score of depression/anxiety, and are less likely to be screened as having depression/anxiety, than ones only receiving standard of care.

My Specific Aims are to:

Aim 1: Perform a systemic review and Meta-analysis about the impact of depression and anxiety disorders on ART initiation among HIV-infected individuals.

Depression disorders have been well studied compared to anxiety disorders among HIV-infected individuals. A meta-analysis offers an opportunity to explore the effect of depression on ART initiation. The impact of depression on ART initiation is inconsistent (J. A. Cook et al., 2007; Goodness et al., 2014; Martinez et al., 2008; B. J. Turner et al., 2001). Hence, we plan to conduct a systemic review and meta-analysis to synthesize results across studies that will provide necessary information for future intervention and prevention on depression. I will also attempt a meta-analysis of anxiety on ART initiation, though there may be fewer available studies. My work will complement a recent meta-analysis of depression and ART adherence (Uthman, Magidson, Safren, & Nachega, 2014).

Aim 2: Assess the effect of depression and anxiety disorders on ART initiation and ART adherence among newly diagnosed HIV-infected MSM during 12 months follow-up in Beijing, China. In the on-going Multi-component HIV Intervention Packages for Chinese MSM (China MP3) project, 367 newly diagnosed HIV-infected Chinese MSM were recruited and randomized into two arms. Participants in the control arm got standard of HIV care (SOC) from local CDC, while participants in the intervention arm received additional peer counseling. We used the Hospital Anxiety and Depression Scales (HADS) to measure depression and anxiety at baseline, 6 months and 12 months. HADS has 7 items to measure anxiety, and other 7 items for depression. The total score of depression/anxiety ranges from 0 to 21 each. To be clinically significant, depression and anxiety were categorized into three groups (0-7 normal; 8-10 borderline;

11-21 likely). When we explored the effect of depression and anxiety on ART initiation and adherence in the context of peer counseling, peer counseling might have an impact on HIV-related outcomes. Therefore, peer counseling was treated as an effect modifier for both hypotheses.

Hypothesis 1: Depression and anxiety disorders can delay ART initiation in newly diagnosed HIV-infected MSM during 12 months follow-up, in Beijing, China. Eligible participants entered into observation at the time point of their first follow-up, and the end point was ART initiation or the end of this study (12 months follow-up). The date of ART initiation was the actual day of their first medicine pick-up, and was extracted from the national HIV/AIDS treatment dataset. Cox Regression was used to calculate the hazard ratio (HR) of depression and anxiety disorders on ART initiation. Depression and anxiety disorders were treated as independent risk factors. Confounding was identified by directed acyclic graph (DAG). A number of other factors were examined for relativeness to ART initiation.

Hypothesis 2: Depression and anxiety disorders are associated with imperfect adherence to ART in newly diagnosed HIV-infected MSM, who initiate ART after HIV diagnosis, in Beijing, China. ART adherence was a self-reported binary outcome. Perfect adherence to ART meant no missing dose in the past three months, and imperfect adherence to ART indicated at least one missing dose in the past three months. As participants took up ART at varied time points, the number of measurements of ART adherence also varied. Mixed-effect logistic model was used to assess such associations between depression/anxiety and ART adherence. Effect modification and confounding were chosen based on literature.

Aim 3: Evaluate the efficacy of peer counseling bundled with SMS on depression and anxiety disorders among newly diagnosed HIV-infected MSM during 12 months follow-up in Beijing, China. Hypothesis 3: Newly diagnosed HIV-infected MSM in the intervention arm with peer counseling are less likely to be screened as having depression and/or anxiety, than ones in the control arm only receiving SOC in China. Newly diagnosed HIV-infected MSM were randomized into control or intervention groups. MSM in the intervention group received a total of 32 short messages at scheduled intervals, which inquired whether participants needed counseling or reminded them of scheduled appointments. Five face-to-face counseling were offered to each MSM in the intervention group. Extra counseling was also available to MSM who asked for it, and peer counselors tried to respond within 24 hours. Participants in the control group only received SOC from the local CDC. HIV-related depression and anxiety was measured at baseline, 6 months and 12 months. For the ordered and categorical depression and anxiety, mixed ordinal logistic regressions were performed.

### **Innovations**

The majority of effort has been put into the prevention of HIV/AIDS among the HIV negative MSM population since the first case of HIV/AIDS found in 1985. However, the HIV positive population is the source of HIV secondary transmission. Targeting on HIV-infected MSM will be able to contribute to the reduction of HIV secondary transmission in a cost-effective way. As we only target less than 10% of the entire MSM population rather than the overall MSM, and it is highly focused and more feasible. HIV

testing linkage-to-care mode is the corner stone for “prevention with positives”. However, the proportion of HIV-infected MSM retained in HIV care is low, given the effort has been put to improve retention rate. Psychological factor can be one of the main reasons for the low retention. Depression and anxiety disorders are the most common mental diseases among PLHIV. However, the prevalence of depression and anxiety disorders in newly diagnosed HIV-infected MSM in China is unknown. In this dissertation, I described the baseline prevalence of depression and anxiety disorders. The trajectory of depression and anxiety disorders over follow-up time was also depicted. I believe this study could provide information for future depression and anxiety intervention among newly diagnosed HIV-infected populations.

The negative effect of depression and anxiety disorders on linkage to care, ART initiation and adherence among PLHIV has been reported. However, evidence is lacking to support such association in newly diagnosed HIV-infected MSM. Hence, I propose to evaluate the impact of depression and anxiety disorders on each step of HIV testing linkage-to-care mode during 12 months follow-up. This study was the first quantitative study to explore the effect of psychological factors on HIV testing linkage-to-care mode among MSM in China.

Our preliminary data showed the prevalence of depression and anxiety disorders was around 30% in newly diagnosed HIV-infected Chinese MSM. Depression/anxiety is a critical issue among newly diagnosed individuals. The standard treatment of major depression is medication. I expect these depressed MSM in our phase II trial has mild depression, as they were just known their HIV sero-positive status within 4 weeks. Support group has been reported as a potential intervention for depressed people. I

assessed whether peer counseling can improve mental health of newly diagnoses HIV-infect MSM during 12 months follow-up.

This study revealed that the mental health status of newly diagnosed HIV-infected MSM in China, and provided evidence on the impact of depression and anxiety disorders on HIV testing linkage-to-care mode. Peer counseling as a potential intervention on depression and anxiety disorder was also examined. Our research could shed light on the future HIV prevention and intervention, especially for the intervention on mental health issues.

## CHAPTER III

### OVERALL STUDY DESCRIPTION

#### **Study design**

The China MP3 project was a two-phase study. The Phase I was a cross-sectional study aiming to expand HIV testing among MSM in Beijing, China. The Phase II study was a pilot randomized clinical trial (RCT) for the evaluation of peer counseling and short message service on the improvement of adherence in the continuum of HIV care, including linkage-to-care, ART initiation and adherence. The overview of our study design was shown in Figure 2. A total of 3,588 eligible participants were enrolled in phase I study, and 455 individuals were diagnosed with HIV infections. We recruited 367 newly diagnosed HIV-infected MSM into the pilot RCT. A block-randomization with stratification by site was used to allocate participants into either intervention or control groups with a 1:1 ratio. Finally, we had 184 men in the intervention arm, and 183 men in the control arm. In this dissertation, I focused on exploring the effect of depression and anxiety on ART initiation and adherence, and evaluating the impact of peer counseling and short message service on depression and anxiety.



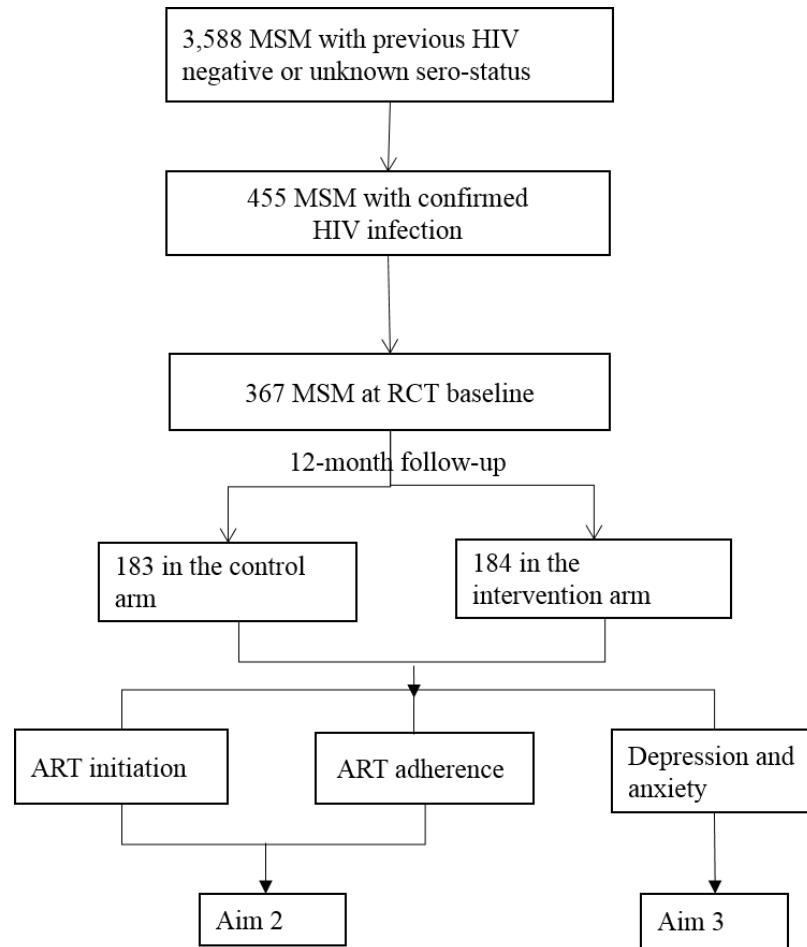


Figure 2 The overall design of our study project

### Study population

The target population was MSM in Beijing, and “MSM” was defined as men who have ever had sex with men. Hence, our study population included gay- and non-gay identified men, bisexuals, male sex workers (e.g., “money boys”), and others who had admitted ever engaging in male-male sexual behavior.

Inclusion criteria for Phase I study were:

- Male, who self-report to have sex with men in the past 12 months;
- At least 18 year-old;
- Living and/or working in Beijing;
- Signed informed consent and willing to take a HIV test;
- Completed the questionnaires;

Inclusion criteria for Phase II study were:

- Diagnosis of HIV infection in phase I study;
- Signed informed consent for the pilot RCT;
- Willing to comply with study procedures;
- No plans to leave Beijing in the next 12 months;
- Having a cell phone and willing to receive study-related SMS texts.

Exclusion criteria are:

- MSM, who self-report a previous HIV positive testing result;
- Unable to comply with scheduled visit and procedures due to psychological disturbance or cognitive impairment, as noted by clinicians.

## **Recruitment**

MSM are hard to reach in China due to stigma and social disfavor. We used multiple sampling methods in order to get a relative representative sample, including short message service, web advertisement, community outreach, and peer referral. A package of short messages was sent to MSM, who were on the listserv of CCAVG

(Chaoyang Chinese AIDS Volunteer Group), to motivate them to participate our Phase I study. These messages briefly introduced the main aims of our project, contact information, our study website and clinics' locations were also included. Advertisements were also posted in several government and gay CBO's websites, including Beijing Municipal CDC ([www.bjcdc.org](http://www.bjcdc.org)), Beijing STD/AIDS Association ([www.aidsonline.com.cn](http://www.aidsonline.com.cn)), STD/AIDS Association ([www.pfxbxh.cn](http://www.pfxbxh.cn)), China Tongzhi Huzhou Group ([www.1tongtuan.com](http://www.1tongtuan.com)), Beijing Tongzhi ([www.tzliao.com](http://www.tzliao.com)), BlueBlood Sky ([www.smsky.org](http://www.smsky.org)), JianAi ([www.hivct.com](http://www.hivct.com)), CCAVG ([www.hivct.org](http://www.hivct.org)), and China Gay ([www.gaycn.net](http://www.gaycn.net)). The advertisements were linked to our Home project website ([www.home.hivct.org](http://www.home.hivct.org)), where MSM could get more information about our project, and schedule a testing visit. Peers in the community based organizations (CBOs) went to gay venues for recruitment, such as gay bars and public gay bathhouses. MSM enrolled our studies were encouraged to refer their male sexual partners or gay friends for taking a test, and they received 5 referral cards, which contained our project aims and contact information. The multiple recruitment approaches were expected to have a relative representative sample of MSM in Beijing.

Newly diagnosed HIV-infected MSM in Phase I study were targeted for Phase II study. We were able to enroll 367 such participants into Phase II study, who also met all the inclusion and exclusion criteria for the RCT. Two clinics were involved in Phase II study, including Xicheng District CDC and Chaoyang District CDC.

## **Intervention**

### Intervention-SMS Check-ins and Peer Counseling

MSM in the intervention arm received SMS check-ins and peer counseling during the 12 months follow-up. Peer counselors (PCs) were chosen from gay-friendly CBOs; they were either HIV sero-positive or sero-negative male volunteers with a homosexual orientation. All PCs in our study were required to complete training on the strategy of education and counseling. We expected PCs could make an effort to improve linkage-to-care, adherence to care, self-adjustment of being HIV positive, risky behavior reduction, and ART initiation and adherence.

The intervention delivered by PCs were monitored by local CDC staff, and a check list was used to make sure that PCs would cover each aspect of intervention by design. There were 5 scheduled face-to-face counseling for participants in the intervention arm. In addition, participants could get extra counseling, when ever needed. SMS check-in was a simple message to check whether participants need counseling, and the context was “Do you want to talk?”. For MSM who replied “Yes”, PCs would contact them and arrange either face-to-face or phone-call counseling. For those who failed to reply within 24 hours, PCs would contact them to check their status. In total, 32 SMS check-ins were sent to participants in the intervention arm at scheduled time via an automatic system during 12 months follow-up.

## Control-standard of Care

Standard of Care (SOC) for PLHIV was offered by government-sponsored institutions, including CDC and public hospitals. The standard of care can vary by sites in Beijing, but it generally included informing of test results, post-test counseling, surveillance reporting, CD4 testing, follow-up, risk reduction and care, and ART referral. Participants in the control arm got SOC provided by local CDC staff. CD4 counts were offered at the time point of HIV diagnosis, and repeated every six months. In addition, participants in the control arm received HIV viral load tests that were not part of the routine SOC.

## **Data collection**

The baseline survey of Phase II study included knowledge about HIV transmission, self-report sexually transmitted diseases (STDs), sexual experience during travel, emotional response to being HIV positive, quality of life, self-efficacy, stigma towards homosexuality and HIV/AIDs, anxiety, and depression. For the follow-ups, the information we measured was shown in Table 1. CD4 counts and viral load testing were offered during 6 months and 12 months follow-up.

Table 1 Frequency of repeated measurements of covariates during 12 months follow-up

Information	3-m follow up	6-m follow up	9-m follow up	12-follow up
Involvement in Interventions and SOC* in the past 3 months	+	+	+	+
Drug and Alcohol Use	+	+	+	+
Sexual Behaviors	+	+	+	+
Self-efficacy	-	+	-	+
Anxiety and Depression	-	+	-	+
HIV-related Stigma	-	+	-	+
Homosexual Stigma	-	+	-	+
Emotional Response to HIV positive	-	+	-	+
Quality of Life	-	+	-	+
CD4 count	-	+	-	+
Viral Load	-	+	-	+

\* Standard of care

#### Quality control on data collection and data entry

We used self-administrated questionnaires to collect information at baseline and each follow-up. Research staff assisted participants to fill in study questionnaire, and reviewed completed questionnaires for missing and out of range values. We used double-blind data entry to minimize errors. We also had a default range for answers to each specific question, and a value out of this range could not be input into our dataset.

The quality assurance (QA) monitor in Vanderbilt Institute for Global Health (VIGH) paid a visit to our study sites, and randomly inspected individual participant's record, such as inform consent, questionnaire, laboratory testing result, and medical records, to make sure the integrity and accuracy of records. QA monitor also checked the daily log at each study site to ensure the compliance with study protocol.

## Laboratory testing

Participants enrolled in Phase II study were all confirmed HIV positive. They were all tested positive in the screening HIV testing-a Rapid HIV test using finger blood in study clinics. Two rounds of enzyme-linked immunosorbent assay (ELISA) with different testing kits were then used to assure positive testing results. HIV infections were confirmed by Western blot assay. Our participants would be informed of testing results within 2 weeks at our clinics. Participants recruited in our Phase II study would have free CD4 count and HIV viral load testing at RCT baseline, 6 months, and 12 months.

### Quality control on laboratory testing

HIV Rapid testing and ELISA were performed by lab technicians at 4 clinics for our phase I recruitment. The four clinics are affiliated to either local CDC or hospital, and all their technicians have been trained to perform rapid test and ELISA. Internal positive and negative controls were required for each run. The original testing results were stored for inspection. In addition, labs at the 4 clinics were required to take part in annually proficiency test (PT) for HIV serological testing organized by National HIV/AIDS Reference Laboratory (NARL), and all of them passed PT in the previous years.

Western blot, CD4 count, and HIV viral load test were performed at Beijing CDC, which is a central HIV/AIDS confirmatory laboratory. This lab is qualified to diagnose HIV new cases, monitor CD4 counts, and assess the eligibility of ART. Internal controls were also added for each test, and the log file and original results were stored. This lab

had an excellent performance at PT for Western blot, CD4+ cell count, and HIV viral load test organized by NARL.



## CHAPTER IV

# ASSOCIATION BETWEEN DEPRESSION AND ANTIRETROVIRAL THERAPY USE AMONG PEOPLE LIVING WITH HIV: A SYSTEMATIC REVIEW AND META-ANALYSIS

### **Abstract**

**Background:** Depression is common among people living with HIV (PLHIV). Studies on the relationship between depression and use of antiretroviral therapy (ART) are inconclusive.

**Methods:** A meta-analysis was conducted to summarize the relationship between depression and ART use in PLHIV. Ten electronic databases and multiple websites of conferences and dissertations were searched. A random effects meta-analysis was performed to pool the odds ratio estimates from eligible studies. Subgroup analyses and meta-regression were conducted for moderator analysis. Sensitivity analysis was performed to find influential studies. A funnel plot, the Egger test, and the trim and fill analysis were used to detect publication bias.

**Results:** The pooled sample size was 7,375 with the inclusion of nine eligible studies. The pooled prevalence of depression was 41% (95% confidence interval [CI]: 29%-53%). The pooled ART use rate was 52% (95% CI: 37%-67%). PLHIV

with depression were 14% less likely (pooled odds ratio [OR]: 0.86; 95% CI: 0.71-1.05) to use ART than those without depression. Subgroup analyses showed that depression was significantly associated with no ART use (pooled OR: 0.84; 95% CI: 0.71-0.99) among studies with a prospective study design (11 populations from 9 studies). Moderator analyses did not show any statistically significant effects. The publication bias analyses showed no evidence of small study effects.

Conclusions: Depression was associated with non-use of ART among PLHIV. Studies are needed to explore this association in other countries with varied populations, as most published studies have been conducted in the United States.

Keywords: Depression; antiretroviral therapy; people living with HIV (PLHIV); meta-analysis; systematic review;

## **Introduction**

Depression is common among people living with HIV (PLHIV). A meta-analysis in 2014 reported that the prevalence of depression among PLHIV was 39% (95% confidence interval [CI]: 33%-45%) (Uthman et al., 2014). Depression is a persistent mood disorder, characterized by feelings of sadness, loss, anger, and frustration that interfere with daily living. Research has shown that depression has a negative impact on HIV testing and care (Bhatia et al., 2011; Mayston et al., 2014; Ramirez-Avila et al., 2012; Traeger et al., 2012). Individuals with depression can experience self-abasement, cognitive impairment, and self-isolation

(Skodol, Schwartz, Dohrenwend, Levav, & Shrout, 1994), which might explain why some depressed PLHIV are less likely to engage in HIV care.

ART is beneficial for both HIV-infected individuals and public health. For individuals, ART can boost the immune system, reduce the chance of opportunistic infections, slow progression to AIDS, and improve HIV/AIDS survival (Croda, Croda, Neves, & dos Santos, 2009; Powderly, Landay, & Lederman, 1998). From a public health perspective, ART can reduce HIV secondary transmission by lowering viral load among PLHIV. HIV testing and care are the key components of the strategy of “Treatment as Prevention” for preventing new infections (Vermund & Hayes, 2013). HIV testing is the gateway to HIV care, and only those who are linked to and retain in care have the opportunity of starting antiretroviral therapy (ART). However, coverage of ART is less than 50% in most countries (Mountain et al., 2014; Mugglin et al., 2012; Wolfe, Carrieri, & Shepard, 2010).

Mental disorders may be a barrier for ART use. Some studies have shown that individuals with depression were less likely to use ART (M. H. Cohen et al., 2004; J. A. Cook et al., 2007; Goodness et al., 2014; Hightow-Weidman, Jones, Phillips, Wohl, & Giordano, 2011; Lillie-Blanton et al., 2010; Martinez et al., 2008; Tegger et al., 2008), while other studies have indicated that depression could increase the likelihood of ART use (Baez Feliciano et al., 2008; Himelhoch, Moore, Treisman, & Gebo, 2004; Mijch et al., 2006). Turner and Fleishman reported that the effect of depression on ART use differed by ethnic group (Turner & Fleishman, 2006). In addition, the prevalence of depression and access to HIV care can vary among different ethnic groups. Given these

disparate reports, we conducted a meta-analysis to summarize the effect of depression on ART use among PLHIV.

## Methods

### Literature search and study selection

A systematic literature search was performed to identify studies that evaluated the relationship between depression and ART use, published between 1996 advent of combination ART and December 15<sup>th</sup>, 2015. Ten electronic databases were searched: BIOSIS Previews (*Biological Abstracts & Biological Abstracts/RRM, Thomson Scientific Technical Support, New York*), Embase (*Elsevier, Amsterdam, The Netherlands*), Ovid Medline (*Ovid Technologies, Inc., New York*), PubMed (*National Center for Biotechnology Information, Bethesda MD*), PsycINFO (*American Psychological Association, Washington*), Scopus (*Elsevier, Amsterdam, The Netherlands*), Web of Science (*Thomson Scientific Technical Support, New York*), CNKI (*Tongfang Knowledge Network Technology Co. Ltd., Beijing, China*), CQVIP (*Chongqing VIP Information Co. Ltd., Chongqing, China*), and Wanfang Data (*Chinese Ministry of Science & Technology, Beijing, China*). CNKI, CQVIP and Wanfang Data were Chinese Databases. We also searched conference abstracts from 2001 to 2015 of *the International AIDS Society (IAS) Conference* (<http://www.abstract-archive.org/>), *Conference on Retroviruses and Opportunistic Infections (CROI)*, and searched dissertations and theses through ProQuest (1996-2015).

We used four main search terms based on the search strings developed by the Cochrane Collaboration. The search strategy for PubMed is listed below:

- (1) HIV/AIDS strings: (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1[tiab] OR hiv-2\*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect\*[tiab] OR human immunodeficiency virus[tiab] OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun\*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[ tiab] OR acquired immuno-deficiency syndrome[ tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun\*) AND (deficiency syndrome[tiab])) or “sexually transmitted diseases, viral”[mh] OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]);
- (2) ART strings: (“antiretroviral therapy, highly active” [MeSH] OR “anti-retroviral agents”[MeSH] OR “antiviral agents”[MeSH:NoExp] OR ((anti[tiab]) AND (hiv[tiab])) OR antiretroviral\*[tiab] OR ((anti[tiab]) AND (retroviral\*[tiab])) OR HAART[tiab] OR ((anti[tiab]) AND (acquired immun\*[tiab]) AND (deficiency[tiab]));
- (3) Use strings: (initiate[tiab] OR initiating[tiab] OR initiation[tiab] OR “when to start”[tiab] OR early treatment[tiab] OR deferred treatment[tiab] OR earlier treatment[tiab] OR use[tiab] OR acceptance[tiab] OR (start\*[tiab] AND therapy[tiab]));

- (4) Depression strings: (depress\* OR dysthymi\* OR anxiety [MeSH] OR anxious[MeSH] OR GAD);
- (5) Published year: "1996"[PDAT]: "2015"[PDAT];
- (6) The strategy was 1&2&3&4&5.

### Study criteria and selection

The criteria for eligible studies are as follows: (1) used any study design; (2) targeted PLHIV; (3) measured depression as an exposure variable; (4) measured ART use as an outcome variable; and (5) provided sufficient information to calculate effect size (ES) estimates. We originally intended a separate assessment of anxiety, but found only one eligible paper.

Studies searched from multiple electronic databases were imported into EndNote 6.0 (*Thomson Reuters Corporation, New York*). Title screening was conducted after removing duplicates. Most irrelevant studies were excluded in this phase. The remaining studies were further screened by reading abstracts. Only studies that mentioned the association between depression and ART use were chosen for full text screening.

### Data extraction

For eligible studies, the following information was extracted in a standardized manner: first author's name, year of publication, study period, study

country, study design, sample size, study population (transmission route), percentage of Caucasians in study population, percentage of male participants, prevalence of depression, method of measuring depression, and method of measuring ART use.

ART use was a self-reported binary outcome in most of the eligible studies. Hence, odds ratios (OR) were used to quantify the association between depression and ART use among PLHIV. People without depression were used as the reference group for the calculation of OR. Several studies also reported the association using risk ratio or hazard ratio; we calculated OR and 95% confidence interval (CI) based on available data for synthesis. If data were not available in the paper, we contacted corresponding authors for related information that could be used for adjusted OR, or raw data that we could use to calculate crude OR.

### Statistical methods

A random effects meta-analysis using inverse variance weights was used to pool effect sizes across eligible studies. The natural logarithm of the odds ratio and its 95% confidence interval were used in the synthesis. We then transformed the overall effect size back into an odds ratio and its 95% confidence interval for ease of interpretation. The meta-analysis results were displayed with forest plots.

To assess heterogeneity among eligible studies, the Q statistic,  $I^2$  statistic, and  $\tau^2$  were used. (Egger, Smith, & Altman, 2001; Higgins, Thompson, Deeks, & Altman, 2003) The Q statistic is underpowered to detect true heterogeneity, given

that a small number of studies are included. Hence, we used a 10% significance level to increase our power to detect heterogeneity using the Q statistic.

To control for the effects of potential moderators and to explore the source of heterogeneity between studies, subgroup analyses and a random effects meta-regression model were conducted. Sensitivity analyses were performed to find influential studies, and we removed one study analysis at a time (11 populations in 9 studies). We used funnel plots, the Egger test, and the trim and fill analysis to assess publication bias. All statistical analyses were conducted in Stata 12.0 (*Stata Corporation, College Station, TX*).

## **Results**

### Results of literature search

Figure 3 shows the process of our study selection. The initial searches in 10 individual electronic databases yielded 3,116 records, and in conference websites, we found 1,042 conference abstracts, of which 1,324 were duplicates and were excluded, leaving 2,834 records for title and abstract screening. Thirty-two publications were identified for full text screening of which 13 reported associations between depression and ART use, and were eligible for our meta-analysis. Two studies did not report enough information to calculate effect sizes (Amiya, Poudel, Poudel-Tandukar, Kobayashi, & Jimba, 2013; Gardner et al., 2002), and two studies had overlapping samples (Judith A. Cook et al., 2002; B. J.



Turner et al., 2001). Hence, nine unique studies were included in our analyses. Two of these studies contributed two estimates of OR, as heterogeneous effects were observed across different study populations (e.g., drug users vs. non-users, and Caucasian vs. Black/Hispanic). Hence, we had 11 effect size estimates in the quantitative synthesis.

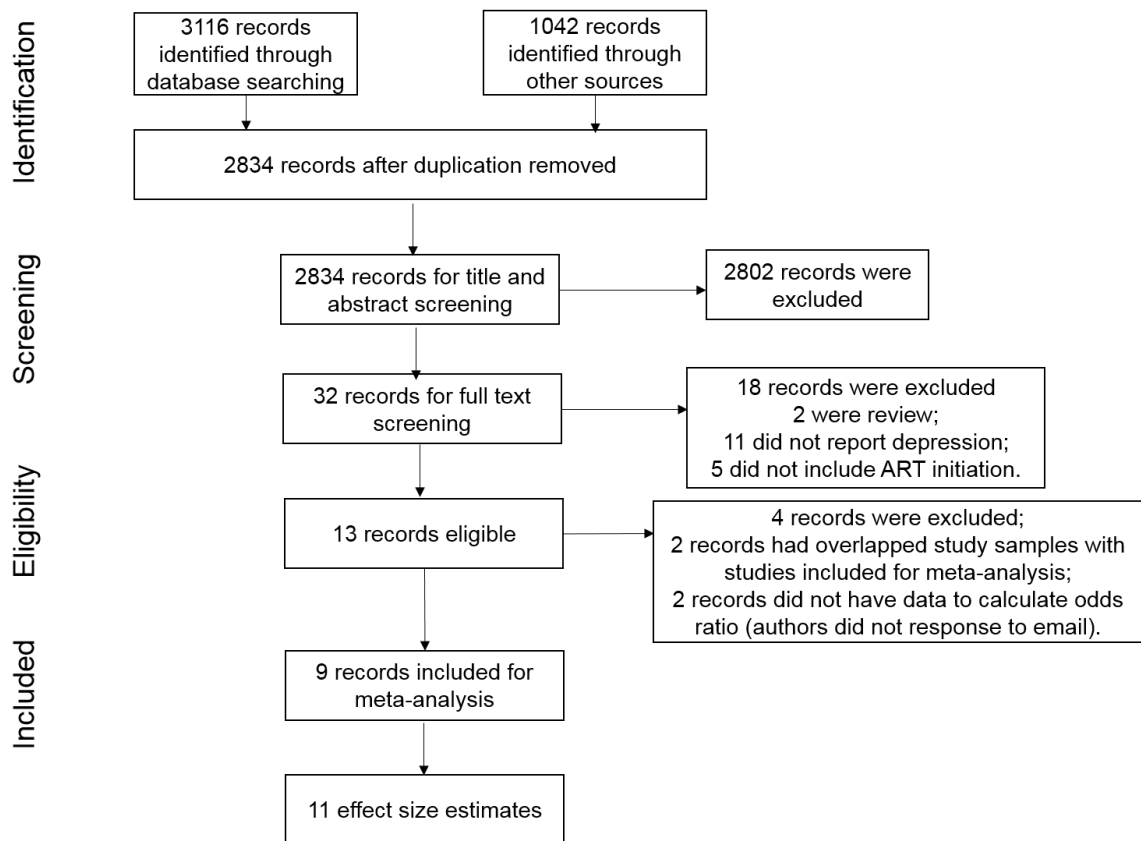


Figure 3 Flow chart of literature selection

## Description of studies

Table 2 summarizes the characteristics of the studies. Of 7,375 pooled study participants, 68% were women, Caucasians represented 30%, and 15% had a CD4+ T lymphocyte (CD4) count less than 350 cells/ $\mu$ L. Seven of nine studies used a scale for screening depression, one study was based on physician's diagnosis (Tegger et al., 2008), and one study used self-reported depressive symptoms (Baez Feliciano et al., 2008). For ART use, six studies used self-report, and the other three studies were based on medical records. Seven studies used a prospective cohort design, and two were cross-sectional. Six of nine studies were conducted in the continental United States, with the other three from Puerto Rico, Uganda, and Russia. All of them were published between 2004 and 2014.

## Effect of depression on ART use

The prevalence of depression ranged from 19% to 77% in the included studies, and the pooled depression prevalence was 41% (95% CI, 29%-53%). ART use rate varied from 11% to 71%, and the pooled estimation was 52% (95% CI, 37%-67%). The pooled synthesis showed that depressed PLHIV were 14% less likely to use ART than those without depression (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.71-1.05; Figure 4). The Q statistic rejected the null hypothesis that the true heterogeneity was due to chance (chis-square: 32.20, degree of freedom=10, *P* value <0.001) at a 5% significance level. The *I*<sup>2</sup> statistic

indicated that 68.9% of variance could be explained by true heterogeneity. The variability of effect sizes ( $\tau^2$ ) across studies was 0.061.

#### Moderator analyses

Table 3 presents results of pooled OR from the subgroup analyses. The synthesized point estimates from studies with a prospective design, studies conducted in the continental United States, and studies using scale screening for depression were similar. The pooled estimate from studies with a prospective study design showed a significant association between depression and ART use (pooled OR, 0.84; 95% CI, 0.71-0.99). The pooled result from studies conducted outside of the continental United States showed a non-significant effect on ART use (pooled OR, 1.04; 95% CI, 0.34-3.17). The difference of pooled effect sizes between the six studies conducted in the continental United States and the three in Puerto Rico, Uganda, and Russia was not statistically significant, when tested in a meta-regression model. In the subgroup analyses by the measurement methods of ART use, the pooled point estimates were different (0.91 for scale screening vs. 0.62 for medical records), and their 95% confidence intervals did not substantially overlap. The pooled point estimate in studies without limitation on CD4 count was 0.91 (95% CI, 0.71-1.17), and the synthesized estimate from studies targeting patients with a CD4 count less than 350 cells/ $\mu$ L was 0.75 (95% CI, 0.55-1.03). However, none of these differences was statistically significant in the random effects meta-regression model.

Table 2. Studies on the relationship between depression and antiretroviral therapy (ART) use among people living with HIV (PLHIV)

Author	Country	Population	Study design	Depression measurement	ART use measurement	Sample size	% of Caucasians	% of males	Depression prevalence (%)	CD4 as ART criteria (cells/ $\mu$ L)
Martinez et al (2008)	Uganda	PLHIV	cross-sectional	Hopkins Symptom Checklist	Medical records	421	0	37	19	All
Tegger et al (2008)	U.S.	PLHIV	prospective	Physician	Medical records	173	53	82	31	<350
Hightow-Weidman et al (2011)	U.S.	HIV-infected young MSM	prospective	CES-D	Medical records	60	0	100	30	<350
Goodness et al (2014)	Russia	HIV-infected heavy drinkers	prospective	BDI-II score	self-report	133	100	53	59	<350
Cook et al among nondrug users (2007)	U.S.	HIV-infected women	prospective	CES-D	self-report	1371	22	0	55	All
Cook et al among drug users (2007)	U.S.	HIV-infected women	prospective	CES-D	self-report	339	22	0	55	All
Cohen et al (2004)	U.S.	HIV-infected women	prospective	CES-D	self-report	750	16	0	45	<350
Turner et al among Whites (2006)	U.S.	PLHIV	prospective	CIDI-SF	self-report	1062	100	84	28	All
Turner BJ et al-among Blacks and Hispanics (2006)	U.S.	PLHIV	prospective	CIDI-SF	self-report	920	0	56	28	All
Lillie-Blanton et al (2010)	U.S. Puerto Rico	HIV-infected women	prospective	CES-D	self-report	1354	14	0	26	All
Feliciano et al (2008)	Rico	HIV-infected PWID	cross-sectional	Self-report	self-report	792	0	84	77	All

Notes: MSM stands for men who have sex with men; CES-D: Center for Epidemiologic Studies Depression Scale; BDI-II: Beck Depression Inventory-II. CIDI-SF: Composite International Diagnostic Interview short-form; PWID: people who inject drugs.

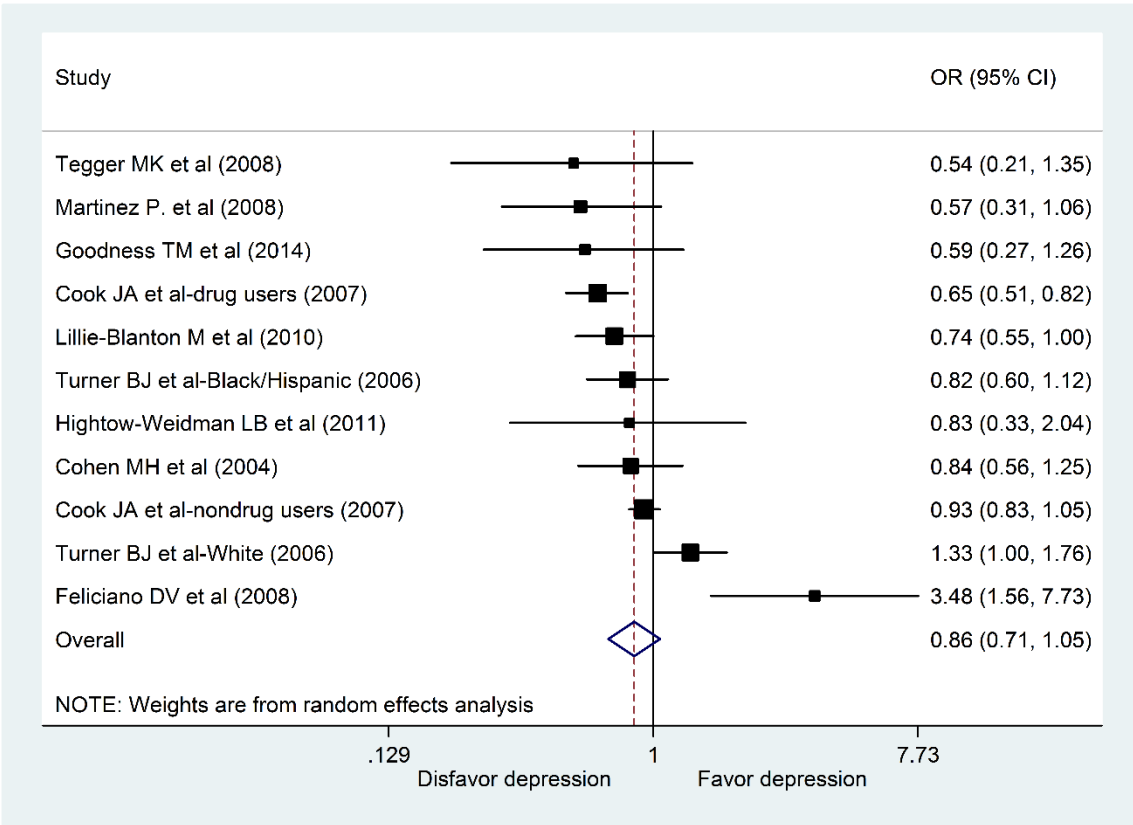


Figure 4 Forest plot of depression on ART use among HIV-infected people

Table 3 Meta-analysis of association between depression and antiretroviral therapy (ART) use in subgroup analysis

Subgroup	No. of populations	Pooled odds ratio (95% confidence interval)
Overall	11	0.86 (0.71, 1.05)
Study design		
Prospective	9	0.84 (0.71, 0.99)
Cross-sectional	2	Not done
Country		
United States	8	0.85 (0.71, 1.01)
Puerto Rico, Russia, Uganda	3	1.04 (0.34, 3.17)
Measurement of Depression		
Scale screening	10	0.83 (0.70, 0.98)
Physician	1	Not applicable
Self-report	1	Not applicable
Measurement of ART use		
Self-report	8	0.91 (0.73, 1.13)
Medical record	3	0.62 (0.39, 0.96)
CD4+ T cell count criterion for starting ART (cells/ $\mu$ L)		
<350	4	0.75 (0.55, 1.03)
No limitation	7	0.91 (0.71, 1.17)

Table 4 Sensitivity analyses of association between depression and antiretroviral therapy use

Removed Studies	Pooled Odds Ratio (95% confidence interval)
Martinez et al (2008)	0.89 (0.72, 1.09)
Tegger et al (2008)	0.88 (0.72, 1.08)
Hightow-Weidman et al (2011)	0.86 (0.70, 1.06)
Goodness et al (2014)	0.88 (0.72, 1.08)
Cook et al among nondrug users (2007)	0.85 (0.66, 1.10)
Cook et al among drug users (2007)	0.90 (0.73, 1.11)
Cohen et al (2004)	0.87 (0.70, 1.08)
Turner et al among White (2006)	0.81 (0.66, 0.98)
Turner et al among Black and Hispanic (2006)	0.87 (0.69, 1.09)
Lillie-Blanton et al (2010)	0.88 (0.71, 1.10)
Feliciano et al (2008)	0.82 (0.69, 0.97)
Overall effect, no study removed	0.86 (0.71, 1.05)

## Sensitivity analyses and publication bias

Sensitivity analyses were conducted to detect influential studies in our meta-analysis. Table 4 lists the pooled odds ratios, with one study at a time removed from the meta-analysis. We found that two studies caused a relative large change on point estimation, and both confidence intervals excluded 1.00, when either was removed (Baez Feliciano et al., 2008; Turner & Fleishman, 2006). This indicated that the two studies were influential studies compared to the rest of the studies included in this synthesis. Notably, Baez Feliciano et al was the only one to report depression based simply on self-report.

For publication bias, the funnel plot was asymmetric (Figure 5). However, the Egger test failed to reject the null hypothesis that no small study effects exist at a 5% significance level. The trim and fill analysis did not yield any trimmed or filled studies. Publication bias is therefore unlikely to exist in this meta-analysis.

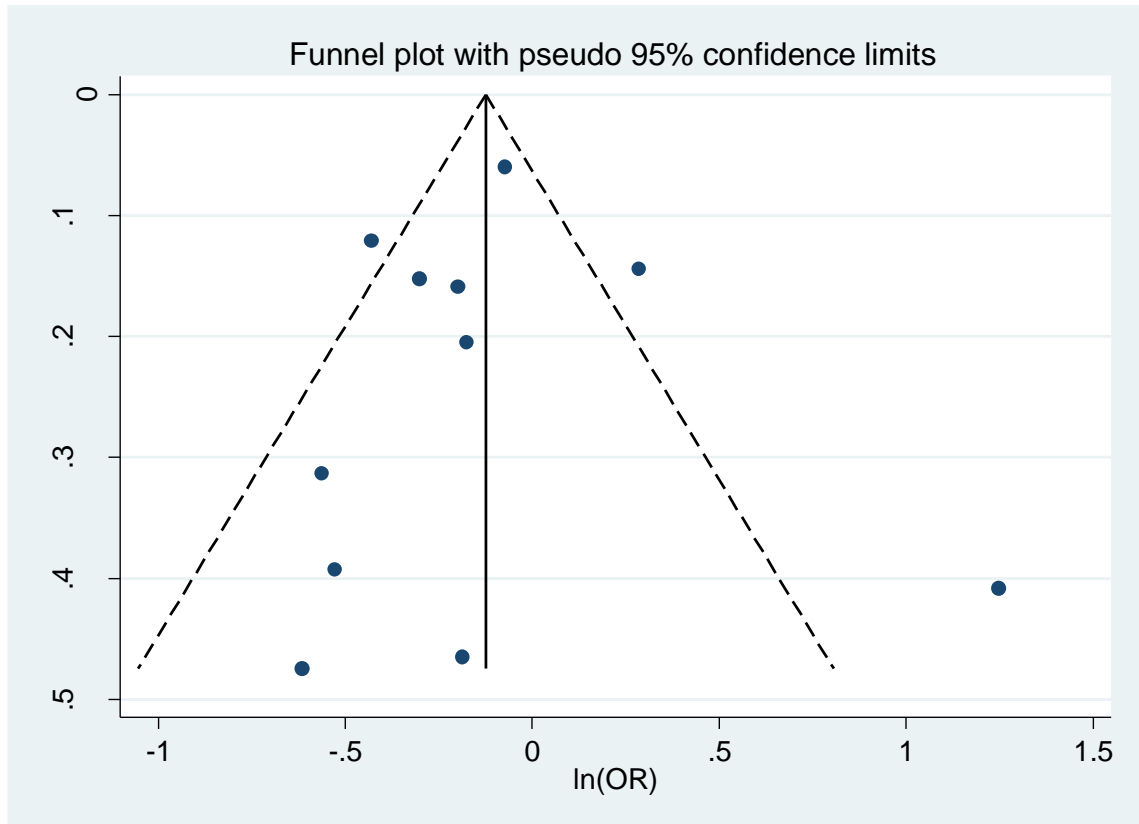


Figure 5 Funnel plot of 11 studies for assessing publication bias.

## Discussion

Our meta-analysis of 11 populations in nine studies including 7,375 PLHIV suggested that depression was associated with a lower likelihood of ART use. Though the overall finding was not significant at a 5% significance level, subgroup analyses showed a statistically significant reduction in ART use among depressed patients in the subset of studies with a prospective study design, or using a scale for depression measurement, or utilizing medical records to assure ART use. Prospective studies could provide more convincing evidence due to the ascertained temporal relationship. Studies with more



rigorous measurements of depression and ART use could reduce reporting bias. Hence, pooled results from these subgroup analyses should be more reliable. Of nine included studies, six were conducted in the continental United States, and three studies (four populations) were from the Women's Interagency HIV Study (WIHS) that contributed significantly to the overall effect (M. H. Cohen et al., 2004; J. A. Cook et al., 2007; Lillie-Blanton et al., 2010). More studies in different regions and populations are needed to provide more evidence for the effect of depression on ART use among PLHIV.

Depression measured among PLHIV is less likely to be a reflection of the immediate emotional reaction to HIV positive status and health concerns, as these studies included participants who had typically known their positive status for years or months. Depressed individuals can experience impairment of cognitive and social functioning (Roca et al., 2015). In such cases, they might be less likely to seek HIV care and initiate ART use (Bhatia et al., 2011; Mayston et al., 2014; Ramirez-Avila et al., 2012; Traeger et al., 2012). Intervention for depression among PLHIV is important to improve their mental health in the long-run, and may have an indirect effect on increasing ART use.

Both depression and ART use rates may vary in different ethnic groups. Some studies found that HIV-infected Caucasians had a higher prevalence of both depression and ART use compared to those of Hispanics and African Americans (Turner & Fleishman, 2006). However, few studies have treated ethnicity as a potential effect modifier. Ethnicity was only considered as a confounding variable for adjustment in most of included studies. Given the potential effect modification of ethnic group, failure to consider this may lead to a misleading combined result, given that the heterogeneous effects exist. Depression and illicit drug use might have a heterogeneous effect on ART

use (J. A. Cook et al., 2007). Most studies in our meta-analysis did not report this potential interaction. Hence, the pooled effect size on depression and ART use can be biased, due to ignoring the potential heterogeneous effects across different groups.

Research has shown that the prevalence of depression among PLHIV can vary among countries with varied income levels (Uthman et al., 2014). Some studies suggested that PLHIV from high- and middle-income countries had higher prevalence of depression than those from low-income countries (Uthman et al., 2014). The coverage of ART use also varied in countries with different income levels ("2013 UNAIDS Report on the global AIDS epidemic," 2013). Six of nine studies included in this analysis were conducted in a high-income country- the United States, so we could not perform a subgroup analysis by country income level. Thus, our study findings may not be generalized to the entire HIV-infected global population, as we did not have a representative sample from countries with varied income levels. We excluded two eligible studies due to incomplete data to calculate effect sizes, and we failed to elicit responses from the authors (Amiya et al., 2013; Gardner et al., 2002). One study was conducted in Nepal, and the other was in the continental United States. If we could add these two studies to our meta-analysis, our results might change.

Heterogeneity assessment suggested that the majority of variance was due to the true heterogeneity. We did not find a significant moderator effect in either the subgroup analyses or Meta regression between different groups (Table 3). A small number of studies in our meta-analysis might limit our power to detect the true difference. In addition, we cannot evaluate the variance within groups, as studies within groups used different methods to measure a certain variables. Take the measurement of depression as

an example. Within the group of studies using scales for screening depression, some studies used the Center for Epidemiologic Studies Depression Scale (CES-D), and others used the Composite International Diagnostic Interview short-form (CIDI-SF) (Table 2). Even though studies used the same scale for depression, they might chose different thresholds for depression (CES-D: 16 vs. 23 as the cutoff value). Self-reported depression is a potentially biased measure. Hence, further studies on depression and ART use with a common measurement method are necessary to provide a more convincing pool estimate.

Publication bias was not noted in this meta-analysis. The Egger test failed to reject small study effects, and the trim and fill analysis did not trim or add a single study. As studies included in our meta-analysis were mostly from the continental United States, studies conducted in other regions might have different results.

In conclusion, our study was the first meta-analysis to evaluate the association between depression and ART use among PLHIV. The evidence suggests that depression is associated with lower uptake of ART, particularly noted in the higher quality studies. As most of studies related to depression and ART use were implemented in the continental United States, more research is needed to provide evidences from other countries with varied ethnicities and income levels, especially low- and middle-income countries.

## CHAPTER V

### IMPACT OF DEPRESSION AND ANXIETY ON INITIATION OF ANTIRETROVIRAL THERAPY AMONG CHINESE MEN WHO HAVE SEX WITH MEN WITH NEWLY DIAGNOSED HIV INFECTIONS

#### **Abstract**

**Background:** Depression and anxiety are common among persons recently diagnosed with HIV infection. We examined whether depression or anxiety were associated with delayed initiation of antiretroviral therapy (ART) in newly diagnosed men who have sex with men (MSM) in China.

**Method:** We conducted a prospective study of Chinese MSM with newly diagnosed HIV infections. The Hospital Anxiety and Depression Scale (HADS) was used for measuring depression and anxiety, with scores of 0-7, 8-10, and 11-21 representing normal, borderline, and likely, respectively. ART initiation information was extracted from the National ART Database. Cox regression was performed to assess associations between HADS scores and the time to ART initiation.

**Results:** Of 364 eligible participants enrolling a median of 11 days after HIV diagnosis, 62% initiated ART during the 12-month follow-up period. The baseline

prevalence for likely/borderline depression was 36%, and likely/borderline anxiety was 42%. In adjusted analyses, compared with a depression score of 0, the hazard of starting ART was 1.82 (95% confidence interval [CI]: 1.38-2.41), 3.11 (95% CI 1.82-5.30), and 2.53 (95% CI: 1.48-4.32) times higher for depression scores of 3, 9, and 13, respectively. A similar pattern was observed for the anxiety score.

**Conclusion:** In contrast to our hypothesis, both depression and anxiety were associated with earlier ART initiation among Chinese MSM with newly diagnosed HIV infections. We speculate that individuals who are more concerned about their new HIV diagnosis may be more likely to seek HIV care and follow a doctor's advice. The effects of depression or anxiety on ART initiation likely differ in varying subgroups and by symptom severity.

**Keywords:** Depression, anxiety, antiretroviral therapy (ART), initiation, men who have sex with men (MSM), newly diagnosed HIV infections, China.

## **Introduction**

UNAIDS estimated that in 2013, 35 million people were living with HIV/AIDS and 2.1 million new HIV infections occurred worldwide (Joint United Nations Programme on HIV/AIDS, 2014). Men who have sex with men (MSM) have been disproportionately represented among HIV/AIDS cases in several regions, such as North and South America and Asia (Dabaghzadeh et al., 2013; Joint United Nations Programme on HIV/AIDS, 2014; Wirtz, 2011). In the United States, 64% of new HIV infections were from MSM in 2012 (Centers for Disease

Control and Prevention, 2015). In China, HIV prevalence in MSM has risen from 0.9% in 2003 to 7.7% in 2014; MSM accounted for 25.8% of new HIV cases in 2014 (Joint United Nations Programme on HIV/AIDS, 2015). Behavioral change and condom promotion have not brought sustained prevention success among MSM.

“Treatment as prevention” is a promising strategy to reduce the likelihood of HIV secondary transmission by lowering viral load. Early and sustained HIV treatment would provide this public health benefit and also reduce opportunistic infections and HIV/AIDS-related death, benefiting the antiretroviral therapy (ART) recipients (F. Zhang et al., 2011; Zolopa et al., 2009). Yet, the coverage of ART is still low among people living with HIV (PLHIV). World Health Organization (WHO) estimated the coverage of ART varied from 5% to 86% across 105 countries with available data in 2013; 84% (88/105) of countries reported coverage lower than 50% ("Antiretroviral therapy coverage data and estimates by country," 2013). Chinese government reported that 59% of diagnosed PLHIV took ART medication in 2014 (Joint United Nations Programme on HIV/AIDS, 2015). A substantial proportion of HIV-infected people do not start ART promptly after HIV diagnosis.

Barriers to ART initiation can emerge from individual, relationship, community, and policy levels (Mugavero, Amico, Horn, & Thompson, 2013). Mental health is an important factor at the individual level, and depression and anxiety are common among PLHIV. A meta-analysis reported a 39% (95% confidence interval [CI]: 33%, 45%) current prevalence of depression among PLHIV (Uthman et al., 2014). Two studies

among HIV-infected MSM showed that the current prevalence of depression was 29% in India and 58% in the United States (Berg, Mimiaga, & Safren, 2004; Sivasubramanian et al., 2011). For anxiety, a prevalence of 24% in India, and 38% in the United States were reported (Berg et al., 2004; Sivasubramanian et al., 2011). HIV-infected MSM may be more prone to depression and/or anxiety due to social isolation and dual stigmatization related to homosexuality and HIV-infection (Stoloff et al., 2013).

Depression has been reported to be associated with delayed initiation of ART among PLHIV (De et al., 2013; Goodness et al., 2014; Martinez et al., 2008; Pence et al., 2008). However, this is not a consistent finding (Baez Feliciano et al., 2008; Himelhoch et al., 2004; Mijch et al., 2006). Depression is also associated with low CD4+ T cell count (CD4 count) and high viral load among PLHIV. CD4 count is used to be an indicator for ART initiation in China. Hence, CD4 count could be a potential mediator for depression and ART initiation. Anxiety is as common as depression in PLHIV, but only one published study has examined its association with ART use (B. J. Turner et al., 2001). No study of depression or anxiety and ART initiation in newly diagnosed persons has been published. In this study, we hypothesized that depression and anxiety would delay ART initiation among Chinese MSM with newly diagnosed HIV infections. Our findings can provided valuable information for depression and/or anxiety intervention among newly diagnosed HIV-infected population in China.

## Methods

### Study design and population

The current study utilized the data from the Multi-component HIV Intervention Packages for Chinese MSM project (China MP3). China MP3 had two phases. In Phase I study, 3,588 Chinese MSM with HIV sero-negative or unknown status were offered free HIV testing in Beijing. Four hundred fifty five (12.7%) were Western blot confirmed as HIV seropositive. These infected participants were then invited to participate in Phase II – a randomized clinical trial (RCT) aiming to assess the effect of peer counseling on HIV linkage to care among Chinese MSM with newly diagnosed HIV infections in Beijing (ClinicalTrials.gov Identifier:NCT01904877). To be eligible, participants in the RCT had to have no intention of leaving Beijing in the next 12 months, and provided informed consent. Enrollment into the RCT occurred a median of 11 days (interquartile range [IQR]: 6-22 days) following the HIV diagnosis. We recruited 367 of the 455 (81%) newly diagnosed MSM into the RCT, which serve as the population for the current study.

### Data collection

Sociodemographic characteristics were collected in Phase I study. Behavioral information was gathered at the baseline survey and at 3-, 6-, 9-, and 12-months follow-up surveys in the RCT. We measured drug and alcohol use, and ART adherence in the past three months in these surveys. Depression and anxiety (Zigmond & Snaith, 1983), quality of life, self-efficacy (J. X. Zhang & Schwarzer,



1995), and stigma related to homosexuality (Neilands, Steward, & Choi, 2008) and HIV/AIDS (Steward et al., 2008) were measured at baseline, and 6- and 12-months of follow-ups only.

#### Measurement of depression and anxiety

The Hospital Anxiety and Depression Scale (HADS) was used to screen current depression and anxiety (Zigmond & Snaith, 1983), which includes seven items for depression and seven items for anxiety. Each item has four responses (scores from 0 to 3). The total possible scores for depression/anxiety range from 0 to 21 each. HADS scores of 0-7 are considered “normal”, scores of 8-10 are defined as “borderline” depression or anxiety, and scores of 11-21 are defined as “likely” depression or anxiety. Categorization can be clinically meaningful, but it assumes that any effect seen is the same within categories, which might not be true. Hence, we used both the categorized and continuous format of depression and anxiety scores to model their relationships with ART initiation.

#### Definition of ART initiation

In our study, we used the date of picking up ART in HIV clinics for the first time to indicate ART initiation. We extracted these dates from the national HIV ART database after the RCT ended. Hence, we could assess all participants’ status of ART initiation in the 12-months follow-up period from the unique

identifiers (identity card number of the People's Republic of China) that guaranteed free ART throughout China. For individuals who initiated ART during the 12-months of follow-up, the observational time was the time interval between the date of enrollment and the date of picking up ART medications for the first time. For those who did not initiate ART within 12-months follow-up, their observational time was the entire follow-up time interval.

### Statistical analysis

Of 367 RCT participants, three (<1%) initiated ART prior to enrollment. They were excluded from the analysis, leaving a sample size of 364. We conducted bivariate analyses to summarize associations between demographic/behavioral variables and ART initiation, which was treated as a binary outcome (yes or no). In primary analyses, the association (summarized by hazard ratios [HR]) between depression/anxiety and the time until ART initiation was estimated using Cox proportional hazards regression models. A priori substantive knowledge, aided by causal graphs, guided the selection of confounding covariates to include in the multivariable models (Hernan, Hernandez-Diaz, Werler, & Mitchell, 2002). These variables included age, study arm (intervention vs. standard of care [SOC]), study site, quality of life, social support, alcohol use, drug use, residency in Beijing, and HIV-related stigma. Depression/anxiety can lead to substance use (alcohol and drug use) and vice versa (Mackie, Conrod, & Brady, 2012). Hence, we performed a sensitivity analysis by specifying a second multivariable Cox models that

included all variables mentioned above but excluded alcohol use and drug use. HIV-related stigma and clinical trial study arm were tested for potential effect modifications. We also examined the linearity of the log-hazards for depression and anxiety scores, age, quality of life, depression/anxiety score, and HIV-related stigma using likelihood ratio tests; when appropriate, restricted cubic splines were used to model non-linear relationships. CD4+ T cell count (CD4 count) is an important indicator for ART initiation, and it could also be on the causal pathway between depression or anxiety and ART initiation (Jane Leserman, 2008). Hence, we additionally adjusted for CD4 count to estimate the direct effect of depression/anxiety (not through CD4 count) on ART initiation. All analyses were performed using Stata 12.0 (*StataCorp LP*, College Station, Texas).

## **Results**

### Demographics of study participants

Among 364 participants, the median age was 28 (IQR: 25-32). Most were of Han ethnicity (93%) and single (84%), had a college education (77%), were employed (83%), and did not have Beijing “Hukou” (or registered household residence; 82%) (Table 5). Over half of participants (55%) had health insurance plan. Fifty-five percent were alcohol users, and 33% reported drug use in the past three months. The syphilis co-infection rate was 14%.

At baseline, the median depression score was 6 (IQR: 3, 9), with depression prevalence of 36% (16% borderline and 20% likely depression). The median anxiety score was 7 (IQR: 3, 10), with anxiety prevalence of 42% (18% borderline and 24% likely anxiety). The prevalence of comorbid depression and anxiety was 32% (117/364) at baseline. Table 6 lists nine combinations of depression and anxiety in our study population. The proportion of individuals with only depression or anxiety symptoms was 11.3%. Depression and anxiety score were highly correlated (Spearman's rank correlation [r]: 0.88,  $p < 0.001$ ).

Table 5. Demographic and behavioral characteristics among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections by initiation of antiretroviral therapy (ART) during 12 months follow-up, in Beijing

Covariates	ART initiation	
	No (N=140)	Yes (N=224)
Age (median, IQR, years)	27 (25, 33)	28 (25, 32)
Study site		
Xicheng Clinic	69 (49.3)	101 (45.1)
Chaoyang Clinic	71 (50.7)	123 (54.9)
Ethnicity		
Han	129 (92.1)	210(93.8)
Others	11 (7.9)	14 (6.2)
Married status		
Single	113 (80.7)	193 (86.2)
Current Married	21 (15.0)	22 (9.8)
Divorced/separated	6 (4.3)	9 (4.0)
Education*		
College education or over	96 (68.6)	183 (81.7)
High school or less educated	44 (31.4)	41 (18.3)
Employment status *		
Employed	107 (76.4)	194 (86.6)
Unemployed or other	33 (23.6)	30 (13.4)
Health care		
Yes	72 (51.4)	129 (57.6)
No	68 (48.6)	95 (42.4)
Place of birth		
Large cities	34 (24.3)	56 (25.0)
Medium cities	31 (22.1)	57 (25.5)
Small cities	32 (22.9)	46 (20.5)
Township/countryside	43 (30.7)	65 (29.0)
Resident in Beijing		
Yes	22 (15.7)	43 (19.2)
No	118 (84.3)	181 (80.8)
Alcohol use in the past three months+		
Never	65 (46.4)	99 (44.2)
Once or more	75 (53.6)	125 (55.8)
Drug use in the past three months		
Never	103 (73.6)	140 (62.5)
Once or more	37 (26.4)	84 (37.5)
Satisfaction with support from friends and/or family members		
Very satisfied	56 (40.0)	95 (42.4)

	Somewhat satisfied	37 (26.4)	71 (31.7)
	Somewhat dissatisfied	20 (14.3)	33 (14.7)
	Very dissatisfied	27 (19.3)	25 (11.2)
Quality of life (Median, IQR)		80 (60, 80)	70 (60, 80)
Depression Score (Median, IQR)		4 (2, 8)	7 (4, 10)
Depression categories			
	Normal (0-7)	104 (74.3)	129 (57.6)
	Borderline depression (8-10)	14 (10.0)	44 (19.6)
	Likely depression (11-21)	22 (15.7)	51 (22.8)
Anxiety Score (Median, IQR)		4 (2, 9)	7 (4, 11)
Anxiety categories			
	Normal (0-7)	93 (66.4)	115 (51.3)
	Borderline anxiety (8-10)	21 (15.0)	46 (20.5)
	Likely anxiety (11-21)	26 (18.6)	63 (28.2)
Syphilis sero-status			
	Negative	117 (83.6)	196 (87.5)
	Positive	23 (16.4)	28 (12.5)
CD4+ T cell count at baseline (cell/ $\mu$ L, Median, IQR)		469 (375, 597)	369 (267, 454)
Viral load at baseline (IU/mL, median, IQR)		38,800 (17, 200, 93,500)	59,900 (26,400, 162,000)
HIV-related stigma (median, IQR)		20 (4, 37)	29 (12, 49)

**Notes:** IQR,

\* P<0.05

† P<0.1

## ART initiation during 12 months of follow-up

During the 12-months of follow-up, 224 of 364 (62%) participants initiated ART, with most (78%) were prescribed the combination of efavirenz/lamivudine/tenofovir. Of the 224 ART initiators, 179 (80%) initiated ART before 3-months of follow-up, 15 (7%) between 3- and 6-months, 19 (8%) between 6- and 9-months, and 11 (5%) between 9- and 12-months. MSM who initiated ART were more likely to be single, college educated, employed, well supported by family members and/or friends, and had a lower baseline CD4 count. Contrary to our hypothesis, they were also more likely to be screened as having depression and/or anxiety (Table 5).

## Association between continuous depression/anxiety scores and ART initiation

As the relationships between the depression or anxiety scores and the log-hazard of starting ART were not linear ( $p < 0.05$  for both), restricted cubic splines were used to model their associations with ART initiation. Neither intervention arm nor HIV-related stigma was an effect modifier for the effect of depression or anxiety on ART initiation. Figures 6(a) and 6(b) show that the hazard of starting ART increased with depression score increasing between 0-7, followed by a nearly flat slope in the score range of 8-10, and then a slowly descending trend with scores between 11 and 21. Figures 6(c) and 6(d) show a similar trends between anxiety scores and the hazard of ART initiation. The median scores in those three

intervals were used in Table 7 to present hazard ratios between depression/anxiety and ART initiation from the various models, with a score of zero as the reference. For the primary model (Model-1) and compared with a depression score of 0, the hazard of starting ART was 1.82 (95% confidence interval [CI]: 1.38-2.41), 3.11 (95% CI 1.82-5.30), and 2.53 (95% CI: 1.48, 4.32) times higher for depression scores of 3, 9, and 13, respectively. For anxiety, a similar pattern was observed except the HRs were slightly less than those for depression (Table 7), with a less steep decline in hazard following a score of 10 (Figure 6). The associations were also very similar regardless of whether or not alcohol and drug use were included as covariates (Model 1a vs. Model 2a).

In our study population, depressed individuals had a lower CD4 count than participants with a normal depression score (median: 355 vs. 407 cells/ $\mu$ L). CD4 count was similarly lower for anxious than non-anxious individuals (median: 362 vs. 407 cells/ $\mu$ L). The additional adjustment of CD4 count in the models of depression/anxiety led to a smaller effect sizes (Table 7). However, the association between depression/anxiety and ART initiation remained strong.

#### Association between depression/anxiety categories and ART initiation

Depression and anxiety are frequently reported as categorical variables. Hence, we also present results with categorized depression/anxiety scores. Figures 7(a) and 7(b) show the cumulative ART initiation rates over the observation time by different categories of depression. Participants with borderline depression were the most likely to



initiate early ART, followed by those with likely depression, and with no depression. The patterns for anxiety were similar to those of depression. Participants with borderline anxiety were more likely to initiate ART at an early time, followed by those with likely anxiety, and those with no anxiety (Figures 7(c) and 7(d)). Table 8 lists hazard ratios of categorical depression/anxiety on ART initiation. Continuous and categorical measurements of depression and anxiety had similar patterns in terms of their effect on ART initiation.

The additional adjustment for CD4 count in models of categorized depression/anxiety did not show a straightforward decrease in hazard ratios across categories (Table 8). In the categories of borderline depression and likely anxiety, there was a smaller effect after adjusting for CD4 count. However, there was an increased hazard ratio for likely depression and borderline anxiety.

Table 6. Frequency of 9 combinations of depression and anxiety categories among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections

Depression	Anxiety		
	Normal (%*)	Borderline (%*)	Likely (%*)
Normal	194 (53.3)	30 (8.2)	9 (2.5)
Borderline	12 (3.3)	25 (6.9)	21 (5.8)
Likely	2 (0.5)	12 (3.3)	59 (16.2)

“\*” percentage by total sample size (N/364).

Table 7. Association between baseline depression/anxiety scores and antiretroviral therapy (ART) initiation among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections

Depression score	Hazard ratio (95% confidence interval)			
	Model-1a	Model-1b*	Model-2a	Model-2b*
3 vs. 0	1.82 (1.38, 2.41)	1.65 (1.25, 2.16)	1.81 (1.37, 2.38)	1.62 (1.23, 2.13)
9 vs. 0	3.11 (1.82, 5.30)	2.65 (1.56, 4.50)	3.10 (1.82, 5.30)	2.63 (1.55, 4.46)
13 vs. 0	2.53 (1.48, 4.32)	2.36 (1.38, 4.03)	2.60 (1.53, 4.43)	2.43 (1.43, 4.14)
Anxiety score	Hazard ratio (95% confidence interval)			
	Model-1a	Model-1b*	Model-2a	Model-2b*
3 vs. 0	1.58 (1.23, 2.04)	1.50 (1.17, 1.94)	1.57 (1.23, 1.99)	1.47 (1.14, 1.89)
9 vs. 0	2.67 (1.59, 4.51)	2.44 (1.44, 4.13)	2.65 (1.60, 4.39)	2.37 (1.40, 4.02)
13 vs. 0	2.49 (1.47, 4.19)	2.37 (1.40, 4.02)	2.54 (1.53, 4.24)	2.39 (1.41, 4.04)

**Notes:** The median scores for participants at normal, borderline, and likely depression/anxiety categories were 3, 9, and 13, respectively. \*Model-1b and Model-2b were results of additional adjustment of CD4 count. By controlling baseline CD4 count- a mediator of depression/anxiety on ART initiation, we attained the direct effect of depression/anxiety on ART initiation.

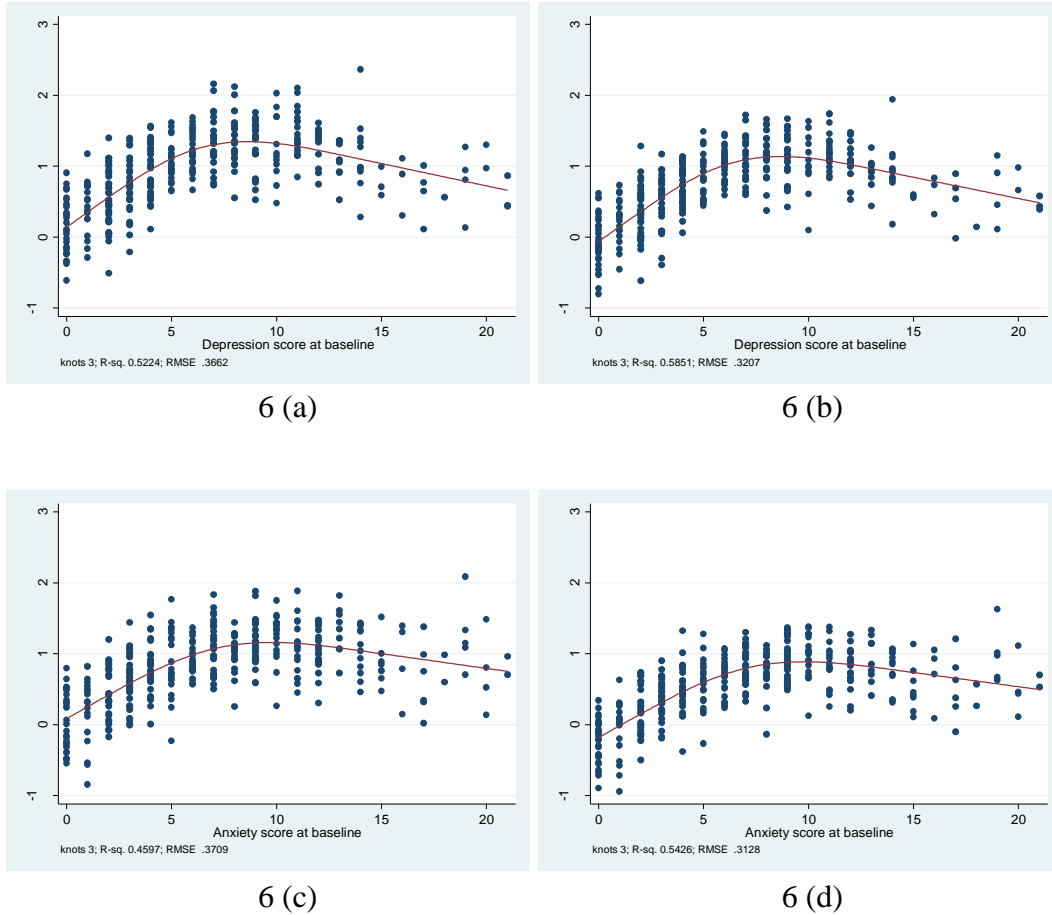
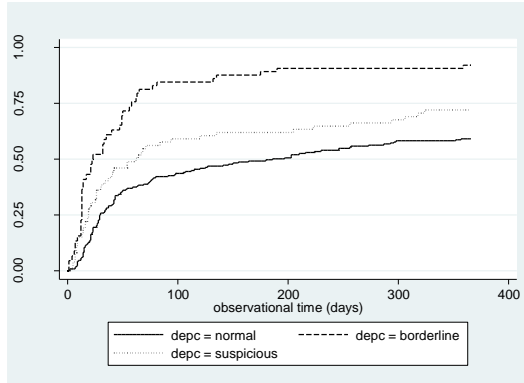


Figure 6. Associations between baseline depression/anxiety scores and hazard of antiretroviral therapy (ART) initiation (log function) among 364 Chinese men who have sex with men (MSM). Figures 6(a) and 6(c) adjusted for age, intervention arm, study site, education, quality of life, living with someone, alcohol use, drug use, residency in Beijing, and HIV-related stigma; Figures 6(b) and 6(d) adjusted for all covariates in 6(a) and 6(c) except alcohol use and drug use.

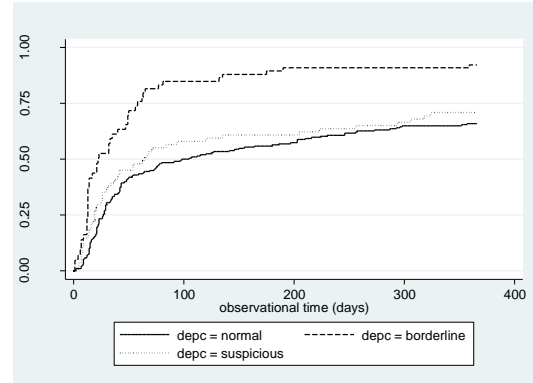
Table 8 Association between categories of depression and anxiety and antiretroviral therapy (ART) among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections.

Depression categories	Hazard ratio (95% confidence interval)			
	Model-1a	Model-1b*	Model-2a	Model-2b*
Normal (0-7)	1.00	1.00	1.00	1.00
Borderline depression (8-10)	1.88 (1.32, 2.67)	1.61 (1.13, 2.29)	1.88 (1.32, 2.67)	1.61 (1.13, 2.30)
Likely depression (11-21)	1.30 (0.88, 1.92)	1.42 (0.97, 2.09)	1.38 (0.94, 2.02)	1.50 (1.02, 2.19)
Anxiety categories	Hazard ratio (95% confidence interval)			
	Model-1a	Model-1b*	Model-2a	Model-2b*
Normal (0-7)	1.00	1.00	1.00	1.00
Borderline anxiety (8-10)	1.27 (0.88, 1.82)	1.28 (0.89, 1.85)	1.28 (0.89, 1.84)	1.30 (0.90, 1.87)
Likely anxiety (11-21)	1.52 (1.05, 2.20)	1.48 (1.03, 2.14)	1.57 (1.09, 2.27)	1.53 (1.06, 2.19)

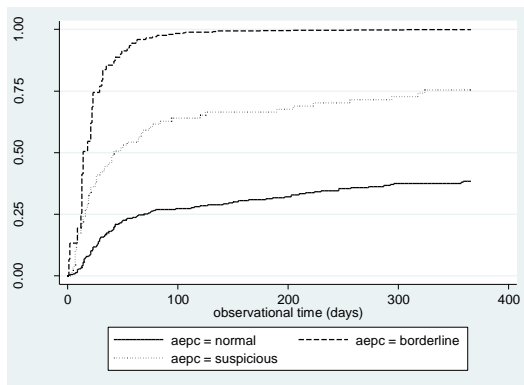
\* Model-1b and Model-2b were results of additional adjustment of CD4 count. By controlling on baseline CD4 count- a mediator of depression/anxiety on ART initiation, we attained the direct effect of depression/anxiety.



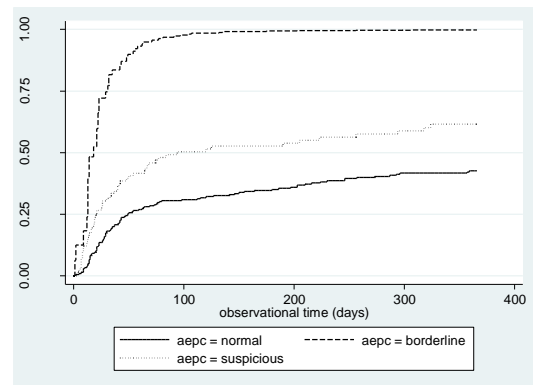
7 (a)



7 (b)



7 (c)



7 (d)

Figure 7. Cumulative probability of antiretroviral therapy (ART) initiation based on depression/anxiety categories among 364 Chinese men who have sex with men (MSM) with newly diagnosed HIV infections. Figures 7(a) and 7(c) are adjusted for age, study intervention, study site, education, quality of life, living with someone, alcohol use, drug use, residency in Beijing, and HIV-related stigma; Figures 7(b) and 7(d) are adjusted all covariates in 7(a) and 7(c) except alcohol use and drug use.

## Discussion

Mental health disorders, especially depression, have been reported to contribute to delays in ART initiation in PLHIV (Alemayehu, Aregay, Kalayu, & Yebyo, 2014; De et al., 2013; Goodness et al., 2014; Murray et al., 2009). We conducted this study to test this hypothesis in Chinese MSM. However, we found a counterintuitive result in that newly diagnosed Chinese MSM with current depression/anxiety were more likely to initiate early ART, although it appeared that participants with more severe depression/anxiety may have been less likely to initiate ART early than participants with borderline depression/anxiety. Three other studies have also reported an increased uptake of ART among depressed individuals (Baez Feliciano et al., 2008; Himelhoch et al., 2004; Mijch et al., 2006).

A meta-analysis has shown that depression itself can decrease CD4 counts—an important indicator for ART initiation (Jane Leserman, 2008). In our study population of newly diagnosed MSM, we did observe that depressed and/or anxious individuals had a lower CD4 count than participants without depression or anxiety. Additional adjustment of CD4 count suggested that CD4 count alone was not sufficient to explain the earlier ART initiation among depressed/anxious participants in our study (Table 7 and Table 8). Other explanations may be responsible for this counterintuitive result, including differences in populations in different studies, the impact of the policy change in China of free ART to all HIV-infected persons regardless of CD4 count, and differing severity of depression/anxiety in different studies.

MSM with newly diagnosed HIV infections in Beijing were a relatively well-educated population. They could learn about HIV-related information via multiple resources (e.g., internet). MSM also had social networks that helped spread information within their communities. Since Beijing MSM might know more about the consequences of HIV infection, depression or anxiety may have been a reflection of their health concerns, nurturing their interest in ART. The Chinese government changed its policy for free ART during our study period; clinicians began to encourage newly diagnosed individuals to initiate ART regardless of CD4 count. It is possible that MSM who were depressed or anxious were given more attention and encouraged to take ART by clinicians. Hence, both patients and practitioners may have influenced early ART in depressed and/or anxious persons.

The severity of depression/anxiety could be another explanation for this discrepancy compared to the literature. HADS performs well in depression/anxiety case finding, but it is not a robust tool to distinguish mild from major depression/anxiety (Bjelland, Dahl, Haug, & Neckelmann, 2002). People with mild depression typically have relatively normal social functioning, while those with major depression have a significant impairment, such as isolation and avoidance of contact (Skodol et al., 1994). Mildly depressed persons are also less likely to have the cognitive impairments that interfere with decision-making. Hence, individuals with mild depression could be more motivated to seek care than ones with major depression, especially if the mild depression is a functional response to concern about their recent HIV diagnosis. Anxiety might be similar. Since we measured

depression/anxiety shortly after the HIV diagnosis, many participants screened as having depression/anxiety may have had an understandable, transient reactive depression/anxiety. Hence, we speculate that our study results may be driven by study design (HADS administered shortly after the HIV diagnosis), and by population characteristics (well-educated MSM).

In our study, 62% Chinese MSM with newly diagnosed HIV infections initiated ART during the 12-months follow-up period. ART coverage in this newly diagnosed population was higher than that reported previously in China (Joint United Nations Programme on HIV/AIDS, 2015), perhaps due in part to the clinical trial nature of our study. In addition, we think that the liberalized policy of free ART treatment in China regardless of CD4 count may have contributed to the increased ART coverage in our study. Research has also shown individuals with a higher education were more likely to initiate ART (Judith A Cook et al., 2007; Martinez et al., 2008). In this study, over 70% of participants had a college education compared to less than 19% in the population of PLHIV in China. Hence, higher education could be another contributor to this high ART coverage.

The comorbidity of depression and anxiety was common in our study population (32%). The depression score was also highly correlated with the anxiety score. Hence, we did not perform mutual adjustment in our analysis due to potential co-linearity. From the viewpoint of mental health interventions, both depression and anxiety should be considered among MSM with newly diagnosed HIV infections.



Our study had several strengths. Firstly, this study was part of a randomized clinical trial, and we performed this analysis as a prospective cohort. Depression/anxiety were measured at baseline, and ART initiation could happen at any time after enrollment. Hence, we have a temporal relationship for the potential causality of depression/anxiety and ART initiation. Archived ART initiation in the national dataset was used for our analysis instead of self-reported ART use. So, we can avoid reporting bias, loss to follow-up, and misclassification of our outcome. Our study population was homogenous, as they were all enrolled in a short time interval after HIV diagnosis. Study sample size was large enough to provide a high power to detect true, meaningful differences.

Our study also had several limitations: our study recruited MSM from a single metropolitan city, and we cannot generalize to the entire MSM population in China. Residual confounding might exist, as we used a proxy for social support for the purpose of confounding adjustment. Our measures of depression and anxiety after HIV diagnosis might not distinguish between reaction of being HIV positive and mental disorders. We cannot estimate the effect of the change of policy of free ART treatment on our study, since it occurred during the time of study conduct.

Early ART initiation has multiple benefits for both individuals and for public health. We found that half of newly diagnosed MSM in our study initiated ART within 3 months of diagnosis. This suggests that it is possible to increase early ART initiation among newly diagnosed persons with interventions both at the policy and individual levels. Depression and anxiety showed unexpected positive effects in terms of ART initiation in our study. Depression and anxiety measured

after HIV diagnosis might be a reflection of being HIV positive and health concern. Hence, we need further studies with a representative sample to replicate our findings in other newly diagnosed populations. We also need to learn the impact of depression and/or anxiety on retention in care and adherence to ART among newly diagnosed PLHIV.

## CHAPTER VI

### EFFECTS OF DEPRESSION AND ANXIETY ON ADHERENCE TO ANTIRETROVIRAL THERAPY AMONG NEWLY DIAGNOSED HIV-INFECTED CHINESE MEN WHO HAVE SEX WITH MEN

#### **Abstract**

Background: Adherence to antiretroviral therapy (ART) is crucial to achieve successful viral suppression in person living with HIV (PLHIV). Depression and anxiety may interrupt patients' adherence with treatment. Yet, little is known about their effects on adherence to ART among men who have sex with men (MSM) with newly diagnosed HIV infection.

Methods: Of 367 Chinese MSM participants in a randomized clinical trial of improved linkage to care, 228 initiated ART after HIV diagnosis and before the end of study, and were included in this analysis. The Hospital Anxiety and Depression Scale (HADS) was used to measure depression and anxiety at baseline, 6 and 12 months. ART adherence was self-reported once every three months (perfect or no missing dose in the past three months vs. imperfect adherence or at least one missing dose in the past three months). We utilized a priori substantial knowledge guided by causal models to identify

confounding covariates, and performed mixed-effect logistic regression to assess the effects of depression and anxiety on ART adherence.

Results: The percentage of perfect adherence to ART was 92% at 3 months, 89% at 6 months, 88% at 9 months, and 88% at 12 months. A one-unit increase in the depression score was associated with a 16% increase in the odds of reporting imperfect adherence to ART (adjusted odds ratio [aOR], 1.16; 95% confidence interval [CI], 1.02-1.32). A one-unit increase in the anxiety score was associated with a 17% increase in the odds of reporting imperfect adherence to ART (aOR, 1.17; 95% CI, 1.03-1.33). When depression and anxiety were categorized (normal, borderline, and likely), the only significant association with adherence to ART was likely anxiety (aOR, 4.79; 95% CI, 1.12-20.50).

Conclusions: Depression and anxiety are risk factors for imperfect adherence to ART among Chinese MSM with newly diagnosed HIV infections. Intensive intervention on depression and/or anxiety beyond regular post HIV-testing counseling may increase adherence to ART, and improve HIV treatment outcomes.

Keywords: Depression; Anxiety; Antiretroviral Therapy (ART); Adherence; Men who have sex with men (MSM); newly diagnosed HIV infections; China

## **Introduction**

“Treatment as Prevention (TasP)” is a promising strategy for HIV prevention and intervention, as it can reduce the risk of HIV secondary transmission by suppressing viral replication (Eaton et al., 2012; Granich et al., 2010). The TasP strategy was first utilized

to control the HIV epidemic among serodiscordant heterosexual couples in China. It has been expanded to Chinese men who have sex with men (MSM), as Chinese MSM have accounted for more than 20% of new cases in each year since 2013 (Joint United Nations Programme on HIV/AIDS, 2015). However, there are several barriers to achieving the expected prevention effect. Maintaining good adherence to antiretroviral therapy (ART) is one of these major challenges (Eaton et al., 2012). A meta-analysis of 111 studies from both developed and developing countries reported an average of 71% of patients had “good” (80% or more doses taken) adherence (95% confidence interval [CI]: 66.0%-75.3%) (Uthman et al., 2014). In China, recent reports suggest that about 77.6% (95% CI, 71.6%-83.1%) report adequate adherence ( $\geq 90\%$ ) in PLHIV (Huan et al., 2016), although the evidence is somewhat mixed with some reports of 80-90% of MSM reporting adequate adherence (Qiao JK, 2014; Zhou YF, Gao MX, Sun YH, Tang H, & Fu Y, 2012). Suboptimal adherence can not only compromise the prevention effect of TasP strategy at the community level, but also lead to drug resistance and viral rebound at the individual level (Glass et al., 2015; Sethi, Celentano, Gange, Moore, & Gallant, 2003).

Mental health disorders may interrupt a patient’s ability to adhere to treatment. Depression and anxiety are of particular concerns among PLHIV who are on ART. The estimated prevalence of depression among PLHIV was 40% (Jeffrey A Ciesla & Roberts, 2014; Lowther, Selman, Harding, & Higginson, 2014; Uthman et al., 2014). Anxiety is also common, 28% as reported in another meta-analysis (Lowther et al., 2014). In MSM with unknown HIV serostatus in Beijing, China, the self-reported lifetime prevalence of depression and anxiety were 11.7% and 18.6% (Yu et al., 2013). Studies have shown that PLHIV are twice likely to be depressed and/or anxious than comparable HIV-negative

persons (J. A. Ciesla & Roberts, 2001). Hence, depression and anxiety would be expected to be more common among HIV-infected Chinese MSM.

Studies have showed that depression and anxiety are associated with poor adherence among PLHIV (Lorenza Nogueira Campos et al., 2010; Gonzalez, Batchelder, Psaros, & Safren, 2011; Nakimuli-Mpungu et al., 2012; Panigrahi, Swain, & Mohanty, 2015; Uthman et al., 2014). Little is known about their prevalence rates and effects on ART adherence among newly diagnosed PLHIV. We conducted this study to fill in these knowledge gaps, and test our hypothesis that depression and anxiety are associated with imperfect adherence (at least one missing dose in the past three months) to ART among Chinese MSM with newly diagnosed HIV infections.

## **Methods**

### Study design and population

The parent study (“Multi-component HIV Intervention Packages for Chinese MSM” or China-MP3 project, ClinicalTrials.gov Identifier: NCT01904877) was a two-phase randomized clinical trial of using behavioral interventions to increase HIV testing and linkage to care. A total of 455 HIV infections were newly identified among 3,588 eligible MSM in Beijing, China in Phase I study, and 81% (367/455) of HIV-infected participants were successfully enrolled into Phase II study – a randomized clinical trial (RCT) that evaluated the impacts of peer counseling and short message service (SMS) interventions on increasing linkage to and retention in HIV care among HIV-infected

MSM in comparison to the standard of care. We assessed the effects of depression and anxiety on ART adherence among a subgroup of MSM participants who initiated ART after HIV diagnosis.

#### Data collection

In Phase I study, we collected baseline data on demographics, drug and alcohol use, and sexual behaviors, as well as laboratory data on HIV and syphilis sero-status. In the RCT, we measured entry to care, initiation of ART, adherence, and drug and alcohol use every three months. We also measured depression and anxiety (Zigmond & Snaith, 1983), quality of life, self-efficacy (J. X. Zhang & Schwarzer, 1995), and stigma related to homosexuality (Neilands et al., 2008) and HIV/AIDS (Steward et al., 2008) every six months.

#### Measurement of depression and anxiety

Depression and anxiety were measured by the Hospital Anxiety and Depression Scale (HADS) - a scale validated for identifying depression and anxiety in multiple populations across countries (Brennan, Worrall-Davies, McMillan, Gilbody, & House, 2010). The HADS has 7 items to measure depression, and another 7 items for anxiety. The score of each item ranges from 0 to 3. Hence, the total scores for depression or anxiety range from 0 to 21 each. The thresholds for categorizing depression and anxiety are 7 and 11: a score of 0-7 is considered “normal”, 8-10 “borderline depression or

anxiety”; and 11-21 “likely depression or anxiety”. Depression and anxiety are commonly used as categorical variables in clinical practice. To avoid categorization leading to low statistical power to detect the true difference by categorizing individuals with heterogeneous effects into the same group, we analyzed the data using both continuous and categorical variables.

#### Measurement of ART adherence

Participants self-reported missing any ART doses in the past three months in the follow-up surveys. We categorized adherence as a binary outcome: perfect adherence indicating not missing any dose, or imperfect adherence meaning missing at least one dose in the past three months. As participants initiated ART at varying time points, the number of measurements of ART adherence varied from 1 to 4 (median 4; interquartile range [IQR] 2-4) among participants.

#### Statistical analysis

We included 228 Chinese MSM who initiated ART after HIV diagnosis, and had at least one measurement of adherence during 12 months of follow-up. Depression and anxiety were also repeated measurements. Mixed-effect models were used to analyze the association between depression and anxiety and ART adherence. Measurements of depression and anxiety at baseline were adjusted in the model, and the next two measurements at 6 and 12 months were treated as time-varying covariates. As we did not



measure depression and anxiety at 3 and 9 months, the measurement of ART adherence at baseline, 6 and 12 months was used in the mixed effects models. For the continuous depression and anxiety scores, restricted cubic splines were used, when the linearity assumption did not hold. A priori substantial knowledge guiding by causal graphs were utilized to determine potential confounding variables (Hernan et al., 2002). Drug and/or alcohol use can have an impact on depression and/or anxiety, and vice versa (Mackie et al., 2012). Hence, we had two sets of confounding variables. The first set included age, study intervention assignment, study site, education, social support, HIV-related stigma, and drug and alcohol use. The second set included all listed variables except drug and alcohol use. We used likelihood ratio test to test whether the study intervention arm (control vs. intervention) and/or HIV-related stigma were potential effect modifiers. All analyses were run using Stata 12.0 (*StataCorp LP, College Station, Texas*).

## **Results**

### Demographics of study population

The median age of 228 eligible Chinese MSM was 28 (IQR: 25-32). Most of them were of Han ethnicity (94%), single (86%), had received at least a college education (82%), and were employed (87%). Around half of our study population (49%) came from small cities or township/countryside. Eighty percent of participants did not have Beijing “*hukou*” (registered household residence). The majority reported having health care insurance (58%), and being satisfied about the support received from family

members and/or friends (74%). In the past three months, 37% of participants reported drug use, and 56% reported alcohol use. At baseline, the prevalence of likely or borderline depression was 43%, and likely or borderline anxiety was 49% (Table 9). The median score for baseline depression was 7 (IQR 4-10), and for anxiety was 7 (IQR 4-11) at baseline. Continuous depression and anxiety scores were highly correlated at baseline (correlation coefficient ( $r$ ) =0.85).

#### ART initiation and adherence

Among 367 enrolled Chinese MSM, 228 individuals (62%) started ART by the end of the RCT. Three of 228 participants initiated treatment after HIV diagnosis, but before enrollment in the RCT. The percentage of self-reported perfect ART adherence was 92% (140/153) at 3 months follow-up, 89% (148/167) at 6 months, 88% (170/194) at 9 months, and 88% (167/189) at 12 months. The number of ART initiators at each follow-up visit varied as per their initiation time points and loss to follow-up (LTFU). By the end of the study, 12% of our study participants were LTFU.

#### Depression and ART adherence

There was insufficient evidence to conclude that the association between depression and the log-odds of depression was non-linear ( $p>0.05$ ). We used the linear depression score in our models rather than restricted cubic splines. Table 10 presents results of associations between depression and ART adherence. In the Model-1, we

observed that a one-unit increase in depression score was associated with a 16% increase in the odds of reporting imperfect ART adherence (adjusted odds ratio [aOR] 1.16; 95% confidence interval [CI] 1.02-1.32). The association was similar in the Model-2 (aOR 1.13; 95% CI 0.99-1.29).

When depression scores were collapsed into categories, all point estimates indicated that depression was a risk factor of self-reported imperfect ART adherence in all models (Table 10). However, none of these associations was statistically significant. In the Model-1 and Model-2, likely depression had a relative large effect on ART adherence in its magnitude of association, when compared to borderline depression.

#### Anxiety and ART adherence

The linear anxiety score was utilized in our analyses, as the linearity assumption held. Results from analyses were presented in Table 10. We found that a one-score increase in anxiety score was associated with a 17% increase (aOR: 1.17, 95% CI: 1.03, 1.33) in the odds of reporting imperfect ART adherence in the Model-1. The result from Model-2 was similar to that from Model-1 (Table 10).

Results from models using the categorical designation of anxiety also suggested that anxiety was associated with imperfect ART adherence. For likely anxiety, we observed a strong and significant association with the point estimates ranging from 4.79 to 4.83 in the Model-1 and Model-2. Individuals with borderline anxiety were 85% more likely to report imperfect ART adherence than ones without anxiety, but this association was not significant in any model.

Table 9. Demographics, behaviors, and health status among 228 Chinese men who have sex with men (MSM) who initiated antiretroviral therapy (ART)

Variable	No. of participants (%)
Age, year (median, IQR)	28 (25-32)
Ethnicity	
Han	214 (93.9)
Other	14 (6.1)
Marital status	
Single	196 (86.0)
Currently married	23 (10.1)
Divorced or separated or widowed	9 (3.9)
Education	
College education or above	187 (82.0)
High school or less	41 (18.0)
Employment status	
Employed	198 (86.8)
Unemployed or other	30 (13.2)
Health care	
Yes	132 (57.9)
No	96 (42.1)
Place of birth	
Large city	59 (25.9)
Medium city	58 (25.4)
Small city	46 (20.2)
Township/countryside	65 (28.5)
Beijing <i>Hukou</i> (legal local residency)	
No	183 (80.3)
Yes	45 (19.7)
Alcohol use in the past three months	
No	100 (43.9)
Yes	128 (56.1)
Drug use in the past three months	
No	144 (63.4)
Yes	83 (36.6)
Social support	
Very satisfied	96 (42.1)
Somewhat satisfied	73 (32.0)
Somewhat dissatisfied	34 (14.9)
Very dissatisfied	25 (11.0)

Syphilis serostatus		
	Negative	200 (87.7)
	Positive	28 (12.3)
Depression score at baseline		7 (4, 10)
Depression status at baseline		
	Normal	130 (57.0)
	Borderline depression	46 (20.2)
	Likely depression	52 (22.8)
Anxiety score at baseline		7 (4, 11)
Anxiety status at baseline		
	Normal	117 (51.3)
	Borderline anxiety	46 (20.2)
	Likely anxiety	65 (28.5)
HIV-related stigma at baseline (Median, IQR)		30 (12, 48)

**Note:** IQR, interquartile range;

Table 10. Association between depression and anxiety and adherence to antiretroviral therapy (ART) among Chinese men who have sex with men (MSM) who initiated ART

Depression/anxiety	Crude odds ratio ([OR], 95% Confidence interval[CI])	Adjusted OR (95% CI)	
		Model-1*	Model-2†
Depression continuous score (0-21)	1.14 (1.01, 1.30)	1.16 (1.02, 1.32)	1.13 (0.99, 1.29)
Depression Categories			
Normal (0-7)	1.00	1.00	1.00
Borderline depression (8-10)	2.14 (0.57, 8.10)	1.74 (0.48, 6.29)	1.68 (0.47, 5.97)
Likely depression (11-21)	1.87 (0.45, 7.84)	1.77 (0.43, 7.37)	1.80 (0.43, 7.50)
Anxiety continuous score (0-21)	1.16 (1.02, 1.33)	1.17 (1.03, 1.33)	1.15 (1.01, 1.31)
Anxiety categories			
Normal (0-7)	1.00	1.00	1.00
Borderline anxiety (8-10)	2.06 (0.60, 7.13)	1.85 (0.56, 6.13)	1.85 (0.56, 6.13)
Likely anxiety (11-21)	5.87 (1.32, 26.13)	4.79 (1.12, 20.50)	4.83 (1.12, 20.71)

\* Model-1 adjusted for age, intervention, study site, education, social support, alcohol use, drug use, and HIV-related stigma; † adjusted for all variables listed in the Model-1, except alcohol and drug use.

## Discussion

Our study found that both depression and anxiety were risk factors for imperfect ART adherence among Chinese MSM with newly diagnosed HIV infections. This is consistent with prior findings in PLHIV from a variety of venues and backgrounds (Gonzalez et al., 2011; Nakimuli-Mpungu et al., 2012; Uthman et al., 2014). A one-unit increase in the depression score was significantly associated with imperfect ART adherence, and the strength of association (aOR 1.16; 95% CI 1.02-1.31) was higher than reported previously from Brazil (aOR 1.04; 95% CI 1.01-1.06) (Tufano, Amaral, Cardoso, & Malbergier, 2014). We used HADS to measure depression among newly diagnosed Chinese MSM in our cohort study, while the Brazilian study used the Hamilton Rating Scale for Depression (HRSD) to assess depression in PLHIV in a cross-sectional study (Tufano et al., 2014). This may lead to the difference in the magnitude of the effect size. Even though we did not find significant associations between categorical depression and ART adherence, the point estimates (aOR varying from 1.74 to 1.80) suggested that depression (borderline or likely) was likely associated with imperfect ART adherence.

For anxiety, a one-score increase was associated with a 17% increase in the odds of reporting imperfect ART adherence (aOR 1.17; 95% CI 1.03-1.33). For the categorical anxiety analysis, we only found a significant association between “likely” anxiety and imperfect adherence to ART (aOR 4.79; 95% CI 1.12-20.50). The literature has also reported similar effects of depression and anxiety (categorical) on imperfect adherence to ART (Lorenza Nogueira Campos et al., 2010; Uthman et al., 2014). Loss of statistical power in the categorical analysis could be a potential explanation for nonsignificant

results with wide confidence intervals. The weight of evidence from both continuous and categorical analyses supports the hypothesis that depression and anxiety are associated with lower ART adherence among newly diagnosed Chinese MSM, consistent with findings in other PLHIV.

Depression and anxiety measured right after HIV diagnosis can be a reflection of immediate health concerns. Unlike initiation that just needs a one-time effort, maintaining ART adherence takes a persistent effort. It is presumably hard for patients with sustained depression or anxiety to adhere to ART over months and years. Depressed and/or anxious individuals may lose interest in HIV care, and may be less capable in keeping to daily schedules.

Depression and anxiety are common among Chinese MSM with newly diagnosed HIV infections. The prevalence of depression and anxiety in our study population were similar to those reported in other studies with PLHIV (Jeffrey A Ciesla & Roberts, 2014; Lowther et al., 2014; Uthman et al., 2014). However, our scale-based measurements revealed prevalence of depression and anxiety to be twice those reported among Chinese MSM with a HIV negative or unknown serostatus (Yu et al., 2013). The proportion of MSM with perfect ART adherence was around 90% in all four follow-up visits over 12 months, higher than that reported in HIV-infected people in several meta-analyses (77%) (Jeffrey A Ciesla & Roberts, 2014; Lowther et al., 2014; Uthman et al., 2014). Other studies of ART adherence among Chinese MSM also reported a comparatively high proportion adhering to ART (Qiao JK, 2014; Yu et al., 2013). Education could be possible explanations for this favorable difference. Chinese MSM are a highly educated population with 80% having at least a college education (Qiao JK, 2014; Jun Tao et al.,

2013; Yu et al., 2013). Among Chinese PLHIV as a whole, less than 19% had a college degree. In addition, better educated HIV-infected individuals are more likely to adhere to ART (Amico et al., 2006; Reynolds et al., 2004).

Our study's strengths include its longitudinal study design nested within a randomized clinical trial. Both our exposure (depression and anxiety) and outcome (ART adherence) were repeated measurements, and we had a higher power to detect the true difference. All our study participants were enrolled in a short time interval after HIV diagnosis, that enabled us to draw inferences among MSM who recently learned of their HIV positive status.

There were also several limitations in our study. We recruited MSM from a single metropolitan city Beijing. We cannot generalize our finding to the entire MSM in China. Further studies with a representative samples are needed to replicate our findings. Twelve percent of study participants were LTFU by the end of study. Our results can be either attenuated or overestimated due to LTFU. Reporting bias may be an issue, as adherence to ART was self-reported.

Early ART initiation and perfect adherence to treatment in this newly diagnosed population are critical to achieve successful viral suppression and good treatment outcomes. ART adherence can also contribute to controlling the HIV epidemic among Chinese MSM through reduced infectiousness of HIV-infected persons. Depression and anxiety were associated with reporting imperfect ART adherence. Intensive early intervention targeting depression and anxiety, beyond routine counseling, may help improve ART adherence among newly diagnosed Chinese MSM.



## CHAPTER VII

### PEER COUNSELING FOR DEPRESSION AND ANXIETY AMONG NEWLY DIAGNOSED HIV-INFECTED MEN WHO HAVE SEX WITH MEN, IN CHINA

#### **Abstract**

**Introduction:** Peer counseling is a promising intervention strategy for depression and anxiety. We conducted a pilot randomized clinical trial that evaluated the effect of peer counseling on reducing depression and anxiety among newly diagnosed HIV-infected men who have with men (MSM) in China. The dynamic changes for depression and anxiety after HIV diagnosis are described.

**Methods:** A total of 367 Chinese MSM with newly diagnosed HIV infections were recruited and randomized into either intervention or control arm. Participants in the control arm received standard of care (SOC) on linkage to care, HIV risk reduction counseling and antiretroviral therapy (ART); while participants in the intervention arm had additional peer counseling (five sessions) during 12 months of follow-up. Depression and anxiety were measured by the Hospital Anxiety and Depression Scale (HADS) at baseline, 6, and 12 months. We used mixed effects models for analysis.

**Results:** Both the score and prevalence of depression and anxiety showed a dramatic decrease at 6 months of follow-up in intervention and control arms. Slight decreasing

trends for the depression and anxiety score were observed only in the intervention arm after 6 months. Peer counseling had a nonsignificant effect on reducing both the depression score (Beta coefficient [ $\beta$ ] -0.22; 95% confidence interval [CI] -0.86-0.41) and the anxiety score ( $\beta$  -0.31; 95% CI-0.96-0.34). Individuals in the intervention arm were 13% (odds ratio [OR] 0.87; 95% CI 0.44-1.69) less likely to be depressed, and were 26% (OR 0.74; 95% CI 0.38-1.47) less likely to be anxious, when compared to those in the control arm.

Conclusions: Depression and anxiety measured right after HIV diagnosis were transient, and could be a reflection of the emotional reaction to discovering their HIV seropositivity. The counseling offered by peer counselors did not significantly reduce depression and anxiety. More intensive counseling and/or medication targeted mental health should be considered among newly diagnosed HIV-infected MSM with persistent depression and/or anxiety.

Keywords: Peer counseling; depression; anxiety; men who have sex with men (MSM); newly diagnosed HIV infections; randomized clinical trial; China

## **Introduction**

Mental disorders are a critical issue among people living with HIV (PLHIV), especially depression and anxiety. The prevalence of depression reported in a meta-analysis was 39% among PLHIV (Uthman et al., 2014), and the prevalence of anxiety was 28% (Lowther et al., 2014). Men who have sex with men (MSM) are a high risk group for mental disorders due to experiencing dual stigma of homosexuality and HIV

infection (Stoloff et al., 2013). In China, the prevalence of HIV infection in MSM reached 7.7% in 2014 (Joint United Nations Programme on HIV/AIDS, 2015). The prevalence of depression and anxiety among Chinese MSM with HIV negative or unknown serostatus were estimated to be 11.7% and 18.6%, respectively in a 2013 study (Yu et al., 2013). One might expect an even higher prevalence of depression and anxiety among HIV-infected MSM.

Depression and anxiety has been reported to be associated with the low rate of linkage to HIV care, late antiretroviral therapy (ART) initiation, and suboptimal ART adherence (Bhatia et al., 2011; Mayston et al., 2014; Ramirez-Avila et al., 2012; Traeger et al., 2012). Medication is one of the standard treatment for depression and anxiety. Many HIV-infected individuals with depression and/ or anxiety are underdiagnosed and hence, do not get treatment (Asch et al., 2003). Epidemiologic studies usually utilize scales for screening depression and anxiety, such as the Hospital Anxiety and Depression Scale (HADS) and Center for Epidemiologic Studies Depression Scale (CES-D), providing better validated prevalence estimates.

Peer counseling has been considered as a promising intervention to address mental disorders (Ali, Farrer, Gulliver, & Griffiths, 2015; Dennis, 2014; Leger & Letourneau, 2015; A. Molassiotis et al., 2002; Richter et al., 2014). Peer counseling has also been used in HIV-prevention and treatment, and may offer aspects of support that could ameliorate depression and anxiety among newly diagnosed populations, even if the targets of the intervention are not mental health per se. However, only limited research has explored the effect of peer counseling on reducing depression and anxiety among PLHIV (A. Molassiotis et al., 2002; Richter et al., 2014). We conducted a randomized

clinical trial (RCT) among newly diagnosed HIV-infected MSM in Beijing, China with a primary aim of evaluating the impact of peer counseling on increasing linkage to HIV care and initiation and retention of antiretroviral therapy (ART). In this paper, we reported the impact of peer counseling on depression and anxiety during 12 months of follow-up.

## **Methods**

### Study design and population

This study was a component of the Multi-component HIV Intervention Packages for Chinese MSM project (the China-MP3), which was conducted in Beijing, China during 2013-2015. In Phase I study, 455 of 3,588 Chinese MSM with previously HIV negative or unknown serostatus were confirmed as HIV seropositive. We recruited 367 (81%) Chinese MSM into the trial. Eligible participants in this trial had no intention to leave Beijing for the next 12 months, were willing to comply with study procedures, and provided informed consent. We enrolled men within a median of 11 days (interquartile range [IQR] 6-22 days) after their HIV diagnosis.

### Peer counseling vs. standard of care

We used block randomization (size=4) was utilized to assign study participants into either intervention or control arms with a 1:1 ratio at the two study sites. We had 184 individuals in the intervention arm, and 183 in the control arm. In the control arm, MSM

received the standard of care (SOC) on linkage to care, HIV risk reduction counseling, antiretroviral therapy (ART), and other relevant medical service currently provided by local Centers for Disease Control and Prevention (CDCs) or hospitals in Beijing City. In addition to SOC service, individuals in the intervention arm received additional five face-to-face peer counseling sessions, which included intervention on enhancing linkage to care and engagement in HIV care, sexual risk reduction, ART initiation, and adherence to ART, as well as mental health counseling, and 32 text messages (“Do you need to talk with peer counselors?”) that were sent every week in the first 3 months and then tapered to every two weeks for the left 9 months of follow-up. Additional peer counseling was provided within 24 hours of the request.

#### Data collection and depression measurement

Self-administered questionnaires (paper and pencil) were used to collect demographic, behavioral and mental health data. Demographic information was collected during HIV testing. Behavioral data were gathered at the baseline and 3-months follow-up visits of the RCT. In the RCT, we measured depression and anxiety (Zigmond & Snaith, 1983), quality of life, self-efficacy (J. X. Zhang & Schwarzer, 1995), and stigma related to homosexuality (Neilands et al., 2008) and HIV/AIDS (Steward et al., 2008) every six months.

## Measurement of depression and anxiety

Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS) at baseline, 6, and 12 months. HADS has 7 items to measure depression, and another 7 items for anxiety. As each item ranges from 0 to 3, the total score of depression/anxiety varies from 0 to 21. There are two recommended thresholds for depression and anxiety. A score of 0-7 indicates normal; 8-10 suggests borderline depression or anxiety; and 11-21 means likely depression or anxiety.

## Statistical analysis

Bivariate analyses were used to describe the demographic and behavioral characteristics between the intervention and control arms. Wilcoxon rank test was performed to test the change of depression and anxiety scores between follow-up periods in each arm. We used linear mixed-effect models to address repeated measurements of the continuous depression and anxiety. For categorical depression and anxiety, mixed-effect ordinal logistic regression models were used. Measurements of depression and anxiety at baseline were included as covariates increasing study power. As our study design was a randomized clinical trial, “intent-to-treat” analysis was used. We reported both the crude effect of peer counseling on depression and anxiety with baseline depression and anxiety measurement as covariates, and the adjusted effect with additional adjustment for

variables with unbalanced distributions between two arms. All analyses were performed using Stata 12.0 (*StataCorp LP*, College Station, Texas).

## Results

### Demographics of study population

Among 367 Chinese MSM, the median age was 28 years (IQR 25-32). Most were of Han ethnicity (93%), single (88%), had a college education (77%), employed (83%), and had no registered household residence in Beijing (“*hukou*”) (82%). Demographic and behavioral variables were balanced between the intervention and control arms by randomization, except for marital status ( $P<0.05$ ), and three other variables with marginal significance ( $P<0.1$ ) -education, having health insurance, and illicit drug use in the past three months. Individuals in the intervention group were more likely to be single, college-educated, have health insurance, and report illicit drug use in the past three months. By the end of 12 months follow-up, the retention rate was 93% in the intervention group, but only 77% in the control group ( $P<0.001$ ). Individuals screened as being depressed at baseline in the control arm were twice more likely to be lost to follow-up (LTFU) by the end of 12 months than those in the intervention arm (17% [11/66] in the control arm vs 7% [5/67] in the intervention arm,  $P=0.19$ ).

## Depression and anxiety during 12 months follow-up

Among 367 Chinese MSM, the median depression score was 6 (IQR 3-9), and the median anxiety score was 7 (IQR 3-10) at baseline. Both depression and anxiety score had a significant decrease in both arms at 6 months of follow-up (Figure 8(a) and 8(b)). A slight descending trend ( $P=0.07$ ) was observed only in the intervention group after 6 months. (Figure 8 (a) and 8(b)).

At baseline, 36% of individuals were classified as being depressed (16% for borderline depression, and 20% for likely depression, Table 11), and 43% of study participants were screened as being anxious (18% for borderline anxiety, and 25% for likely anxiety, Table 11). Similar to what we observed for the depression and anxiety scores, we observed a dramatic decrease in the percentage of individuals being depressed or anxious at 6 months follow-up (Table 11). However, the percentage of MSM having depression and/or anxiety did not change markedly at 12 months follow-up (Table 11).



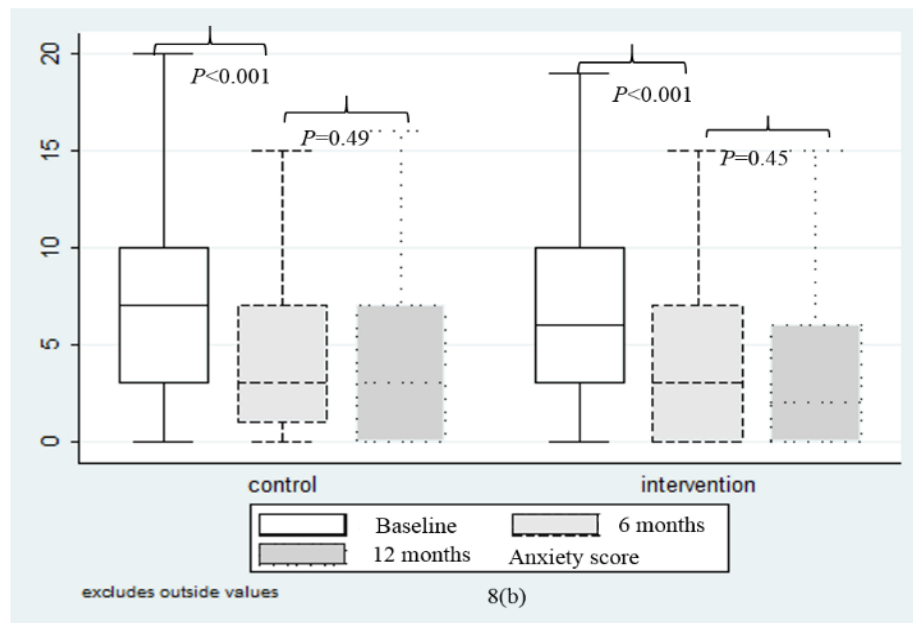
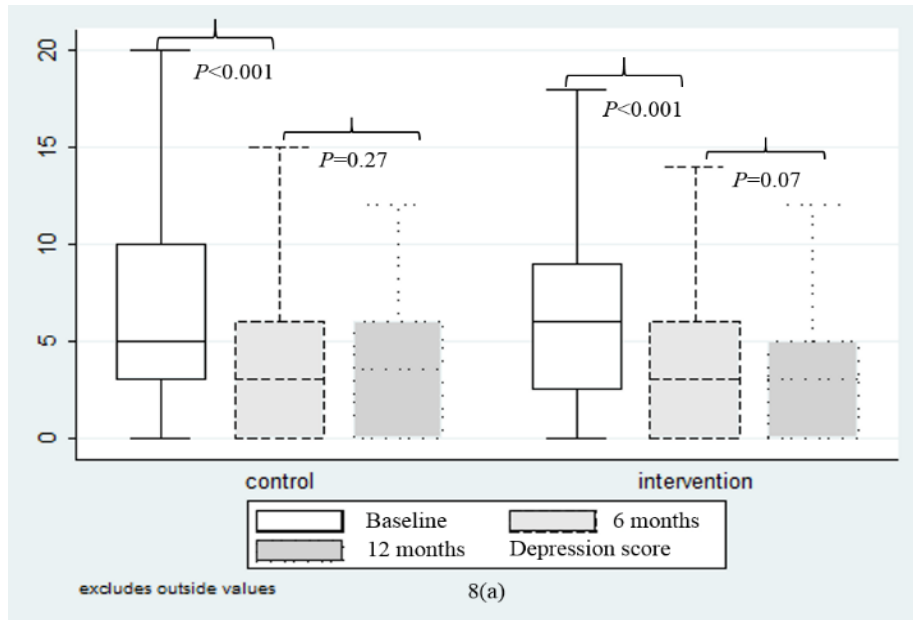


Figure 8. Box plot of the depression/anxiety score by study arm among 367 newly diagnosed HIV-infected Chinese men who have sex with men (MSM) during 12 months of follow-up. 8(a) the depression score; 8(b) the anxiety score.

Table 11. Prevalence of depression and anxiety by study arm among 367 newly diagnosed HIV-infected Chinese men who have sex with men (MSM) during 12 months of follow-up

Depression (HADS)	Baseline		6 months follow-up		12 months follow-up	
	Control (N=183)	Intervention (N=184)	Control (N=159)	Intervention (N=172)	Control (N=140)	Intervention (N=171)
Normal (0-7)	117 (63.9)	117 (63.6)	130 (81.7)	148 (86.1)	121 (86.4)	145 (84.8)
Borderline (8-10)	28 (15.3)	31 (16.8)	16 (10.1)	15 (8.7)	10 (7.1)	15 (8.8)
Likely (11-21)	38 (20.8)	36 (19.6)	13 (8.2)	9 (5.2)	9 (6.5)	11 (6.4)
All depression (8-21)	66 (36.1)	67 (36.4)	29 (18.3)	24 (13.9)	19 (13.6)	26 (15.2)
<b>Anxiety (HADS)</b>						
Normal (0-7)	98 (53.6)	112 (60.9)	123 (77.4)	141 (82.0)	111 (79.3)	143 (83.6)
Borderline (8-10)	40 (21.8)	27 (14.7)	20 (12.6)	23 (13.4)	20 (14.3)	21 (12.3)
Likely (11-21)	45 (24.6)	45 (24.4)	16 (10.0)	8 (4.6)	9 (6.4)	7 (4.1)
All anxiety (8-21)	85 (46.4)	72 (39.1)	36 (22.6)	31 (18.0)	29 (20.7)	28 (16.4)

HADS: Hospital Anxiety and Depression Scale.

#### Effects of peer counseling on depression and anxiety

Even though we observed a decreasing trend in the depression score and percentage of MSM with depression over time, there were no statistical differences between the intervention and control arms in terms of the reduction of depression score and depression prevalence over time. After controlling for baseline depression score and time from randomization, depression scores in the intervention arm were 0.22 (95% confidence interval [CI] -0.86-0.41) lower on

average than scores in the control arm (Table 12). Chinese MSM in the intervention arm were 13% (odds ratio [OR] 1.13, 95% CI 0.44-1.69) less likely to be depressed (borderline and likely depression) compared to those in the control arm. When we additionally adjusted for the unbalanced variable of “marital status”, the adjusted odds ratio was 0.99 (95% CI 0.50-1.96).

The effect of peer counseling on anxiety was similar to its effect on depression. The difference of reduction in the score and prevalence of anxiety between two study arms was minimal. After controlling for baseline anxiety score and time from randomization, anxiety scores in the intervention arm were 0.31 (95% CI -0.96-0.34) lower on average than scores in the control arm (Table 12). Chinese MSM in the intervention arm were 26% (aOR 0.74, 95% CI 0.38-1.47) less likely to be anxious (borderline and likely depression) compared to those in the control group. Further adjustment for marital status attenuated this association (Table 12).

Table 12. Effect of peer counseling on depression and anxiety among 367 newly diagnosed HIV-infected Chinese men who have sex with men (MSM) during 12 months of follow-up

Outcomes	Peer counseling			
	Crude Beta coefficient (95% confidence interval [CI])	Adjusted Beta coefficient (95% [CI])	Crude Odds ratio (OR) (95% CI)	Adjusted OR (95% CI)*
<i>Continuous format</i>				
Depression	-0.22 (-0.86, 0.41)	-0.14 (-0.77, 0.50)	-	-
Anxiety	-0.31 (-0.96, 0.34)	-0.23 (-0.88, 0.42)	-	-
<i>Ordinal categorical format</i>				
<b>Depression</b>				
Borderline & suspicious depression vs. normal	-	-	0.87 (0.44, 1.69)	0.99 (0.50, 1.96)
<b>Anxiety</b>				
Borderline & suspicious anxiety vs. normal	-	-	0.74 (0.38, 1.47)	0.83 (0.42, 1.65)

\*adjustment for marriage.

## Discussion

In our study, we found that both the depression and anxiety scores and the percentage of MSM who were classified as depressed and/or anxious dramatically decreased at 6 months follow-up compared to baseline shortly after HIV diagnosis. Depression and anxiety levels remained fairly constant from 6 to 12 months after HIV diagnosis. Depression and anxiety at baseline are likely a reflection of the immediate emotional reaction to learning of their HIV seropositive status. Chinese MSM must cope with fears related to being HIV positive, feelings of guilt and

embarrass, and sometimes cope with feelings of denial. All these emotions could manifest in transient depression and anxiety. They may need several months to adjust to being HIV positive. Once they can begin to cope with the diagnosis, symptoms of depression and anxiety may diminish.

Peer counseling has been seen as a promising intervention to decrease depression among high risk groups (Ali et al., 2015; Dennis, 2014; Leger & Letourneau, 2015). However, peer counseling did not have a statistically significant effect in this study on the reduction of depression and anxiety among newly diagnosed HIV-infected Chinese MSM during 12 months of follow-up. The fact that peer counseling in our study was not designed specially to target mental health may lead to peer counseling's modest effect on depression and anxiety. The retention rate was higher in the intervention arm compared to that in the control arm (93% vs. 77%), a finding with important implication for the continuum of HIV care. Depressed individuals in the control group were more likely to be LTFU, when compared to ones in the intervention group who have adhered to follow-up, presumably due to peer counselors' influence. Hence, the differential retention rate might lead to the non-significant results due to comparing retained intervention participants to a healthier group of control. Another possible explanation for the non-significant result is that MSM with newly diagnosed HIV infections may be more likely to seek care and help from practitioners due to their concerns about their health. Hence, peer counseling might provide little additional effect on reducing depression and anxiety.

Our study had several strengths. First, it was a randomized clinical trial with a sample size sufficient for adequate power to test the hypothesis. Depression and anxiety were repeated measurements. Hence, we could observe the trend of depression and anxiety after HIV diagnosis. Our study participants were homogenous, as most of them were recruited in a short time interval after HIV diagnosis. The study also had several limitations. The retention rate in the intervention group was much higher than that in the control group, and this could bias comparisons between two groups. MSM were from a metropolitan city-Beijing. Hence, we cannot generalize our results to the entire population of Chinese MSM.

Depression and anxiety can be a transient reaction to the HIV diagnosis. Intervention on depression and anxiety after HIV diagnosis could help newly diagnosed HIV-infected people to cope with their infection status and improve their mental health in the long run. Further studies with a more representative study sample and more intensive peer counseling targeting mental health are needed to verify the effect of peer counseling on depression and anxiety among newly diagnosed HIV-infected population. Improving the HIV continuum of care may benefit from scalable and effective mental health screening and interventions.

## CHAPTER VIII

### SYNOPSIS

This dissertation explored the effects of depression and anxiety on ART initiation and adherence among newly diagnosed HIV-infected Chinese MSM using the data from a randomized clinical trial—the China-MP3 program. There were 4 aims in this dissertation: 1) conduct a meta-analysis on depression and ART initiation; 2) evaluate the effects of depression and anxiety on ART initiation; 3) explore the association between depression and anxiety and ART adherence; 4) assess the impact of peer counseling on the reduction of depression and anxiety.

MSM is a driving force of the HIV epidemic in China. The prevalence of HIV among Chinese MSM shows an increasing trend since 2003 reaching 7.7% nationwide in 2014. In contrast, HIV prevalence in other high risk populations, such as drug users and female sex workers, has a decreasing trend. In the China-MP3 program, we observed that 13% of MSM with a previous HIV negative or unknown serostatus in Beijing were testing positive. Behavioral change and condom promotion have not brought sustained prevention successes among MSM. Hence, effective HIV prevention and intervention strategy are urgently needed to control the HIV epidemic among MSM. “Treatment as prevention” is a promising HIV prevention strategy, as it can reduce the likelihood of HIV secondary transmission by lowering viral load. However, the coverage of ART is suboptimal among Chinese MSM.

Depression and anxiety are common among PLHIV. A 39% prevalence of depression was reported among PLHIV in a meta-analysis with 111 studies from both developed and developing countries. Twenty-eight percent of PLHIV had symptoms of anxiety in another meta-analysis. We intended to conduct a meta-analysis to synthesize the effect of depression and anxiety on ART initiation. As we only found one study that reported the association between anxiety and ART initiation, the meta-analysis were only performed for depression and ART initiation. In our meta-analysis, the pooled prevalence of depression was 41% (95% CI: 29%-53%), and the pooled ART initiation rate was 52% (95% CI: 37%-67%). Depressed PLHIV were 14% (aOR 0.86; 95% CI 0.71-1.05) less likely to initiate ART. When we only included studies with a prospective study design, depression had a significant negative association with ART use (aOR 0.84; 95% CI 0.71-0.99). This association can be influenced by ethnic groups and income-levels. However, we did not have enough information to assess potential moderator effects. As most of the studies were conducted in the United States, more studies in other countries are needed to further explore the effect of depression on ART initiation.

Given its potential importance, the effect of depression on ART initiation among MSM in China was investigated in this dissertation. As a very limited number of studies targeted anxiety and ART initiation, I also explored this association. Early ART initiation in a newly diagnosed population can bring more public health benefits. Targeting newly diagnosed HIV cases can effectively control the source of new infections by reducing the contagious period. Therefore, it is important to evaluate the effect of depression and anxiety on ART initiation in a newly diagnosed population. In my analysis, 62% of study participants initiated ART before 3 months follow-up. In adjusted analyses, compared



with a depression score of 0, the hazard of starting ART was 1.82 (95% confidence interval [CI]: 1.38-2.41), 3.11 (95% CI 1.82-5.30), and 2.53 (95% CI: 1.48-4.32) times higher for depression scores of 3, 9, and 13, respectively. A similar pattern was observed for the anxiety score. I found the counterintuitive result that depression and anxiety can actually promote ART initiation among Chinese MSM with newly diagnosed HIV infections. We speculated that depression and anxiety measured right after HIV diagnosis could be a reflection of immediate health concerns. Depressed or anxious individuals may also get more attention from a healthcare provider, and then more likely to be convinced as to the benefits of early ART initiation. The severity of depression and/or anxiety could be another explanation. Most of newly diagnosed MSM may have mild depression, and they may be more likely to seek care and initiate ART. However, this hypothesis needs further research to verify.

ART initiation and ART adherence are both essential for “treatment as prevention”. Maintaining an optimal ART adherence is critical to achieve successful viral suppression. Depression has been demonstrated to be associated with suboptimal ART adherence among PLHIV. However, we know little about the effect of anxiety on ART adherence. No studies have explored such associations among newly diagnosed populations. In this dissertation, I assessed the associations between depression and anxiety and ART adherence among Chinese MSM with newly diagnosed HIV infections. The percentage of perfect adherence to ART was 92% at 3 months, 89% at 6 months, 88% at 9 months, and 88% at 12 months. A one-unit increase in the depression score was associated with a 16% increase in the odds of reporting imperfect adherence to ART (adjusted odds ratio [aOR], 1.16; 95% confidence interval [CI], 1.02-1.32). A one-unit

increase in the anxiety score was associated with a 17% increase in the odds of reporting imperfect adherence to ART (aOR, 1.17; 95% CI, 1.03-1.33). When depression and anxiety were categorized (normal, borderline, and likely), the only significant association with adherence to ART was likely anxiety (aOR, 4.79; 95% CI, 1.12-20.50). The results were consistent with that in the literature, and indicated that both depression and anxiety were associated with suboptimal ART adherence among newly diagnosed MSM.

In this dissertation, I found that depression and anxiety can increase the likelihood of ART initiation, but have an association with suboptimal ART adherence. Even though these findings seemed contradictory with each other, I believe that these findings are plausible. Depression and anxiety measured right after HIV diagnosis can reflect urgent health concerns. Hence, it is not surprised that newly diagnosed Chinese MSM screened as being depressed and/or anxious could be more likely to initiate ART. Unlike the one-time effort to begin ART, adherence to treatment needs persistent efforts to take medicine every day. Depressed and/or anxious individuals may lose interest and feel interfered within their daily lives, finding that it is hard to keep to schedules. Hence, we were not surprised that they were more likely to miss doses.

Depression and anxiety can suppress the immune system, speed up AIDS progress, and increase AIDS mortality. They are also barriers for HIV testing and linkage-to-care. Therefore, interventions for depression and anxiety are needed for PLHIV. Medication is one of the standard treatment for most mental health woes. However, medications are only available for patients diagnosed by physicians. In fact, a lot of depressed or anxious HIV-infected individuals are underdiagnosed. Hence, alternative intervention strategies are needed to target mental disorders among PLHIV.

Peer counseling has been considered as a promising intervention for mental disorders. In this dissertation, I assessed the impact of peer counseling on reducing depression and anxiety among Chinese MSM with newly diagnosed HIV infections. Both the score and prevalence of depression and anxiety showed a dramatic decrease at 6 months of follow-up in both groups. Slight decreasing trends for the depression and anxiety score were observed only in the intervention group after 6 months. Peer counseling had a nonsignificant effect on reducing both the depression score (Beta coefficient -0.22; 95% confidence interval [CI] -0.86-0.41) and the anxiety score (Beta coefficient -0.31; 95% CI-0.96-0.34). Individuals in the intervention group were 13% (odds ratio [OR] 0.87; 95% CI 0.44-1.69) less likely to be depressed, and were 26% (OR 0.74; 95% CI 0.38-1.47) less likely to be anxious, when compared to those in the control arm.

However, peer counseling did not significantly reduce depression and anxiety during 12 months follow-up in this analysis. Several reasons might lead to this null result. First, peer counseling in this randomized clinical trial did not target mental health per se. Depressed or anxious individuals in the control group were more likely to be LTFU. Peer counseling may not have a greater effect on depression and anxiety beyond what SOC offered than the healthier participants. We also found that the score of depression and anxiety had a dramatic decrease at 6 months follow-up in both intervention and control groups. This indicated that depression and anxiety measured right after HIV diagnosis were transient, and could be a reflection of emotional reactions of discovering HIV seropositivity and/or other health concerns.

Depression and anxiety are critical issues among Chinese MSM with newly diagnosed HIV infections. For individuals, they can contribute to a poor AIDS prognosis with delayed ART initiation and suboptimal ART adherence. From perspectives of public health, they could be an obstacle for “treatment as prevention”. Hence, interventions targeted depression and anxiety after HIV diagnosis are urgently needed to improve individuals’ lives and the effect of “treatment as prevention”. Interventions on depression and anxiety can have an impact on increasing the rate of HIV testing and linkage-to-care, and contribute much to curb the HIV epidemic in China.

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