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Applying Health Stigma Framework to Examine the Mechanisms Of HIV-Related Stigma on Clinical Outcomes

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APPLYING HEALTH STIGMA FRAMEWORK TO EXAMINE THE MECHANISMS OF HIV-RELATED STIGMA ON CLINICAL OUTCOMES

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DEDICATION

I dedicate this dissertation to my parents, Shuchao Zeng and Kui Song; my grandparents, Jiayao Song and Feng Chen; and my old friends, Yongkang Chen, Rongjie Huang, and Churan Zhou for the unconditional love, support, and encouragement.

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ABSTRACT

Background: HIV clinical outcomes including CD4 count, viral suppression, and health-related quality of life (HRQoL), are important indicators reflecting immunologic functioning, treatment efficacy, and overall health quality. However, due, in part, to HIV-related stigma, many people living with HIV (PLWH) experience suboptimal clinical outcomes. The Health Stigma Framework introduced the potentially distinct mechanisms underlying internalized, anticipated, enacted stigma and health outcomes through psycho-behavioral pathways. Based on this framework, this dissertation investigated the impacts and mechanisms of HIV-related stigma on clinical outcomes among PLWH in Guangxi, China from a longitudinal perspective.

Methods: Data at baseline, 6-, 12-, 18- month follow-ups were derived from a prospective cohort study among 1,198 in Guangxi, China. Hierarchical generalized linear mixed model was employed to test the separate impacts of internalized, anticipated, and enacted stigma on each clinical outcome after accounting for psycho-behavioral factors (i.e., antiretroviral therapy [ART] self-efficacy, HIV symptom management self-efficacy, ART adherence) and covariates. Latent growth curve modelling and mediation analysis were employed to examine the mediating effects of psycho-behavioral factors between stigma and each clinical outcome.

Results: In hierarchical generalized linear mixed models, internalized, anticipated, and enacted stigma showed negative impacts on HRQoL but these impacts were not found in

CD4 count and viral suppression. Mediation analyses revealed that ART self-efficacy and ART adherence mediated the indirect pathways from HIV-related stigma to viral suppression but these effects were not found in CD4 count. ART self-efficacy consistently mediated the impacts of the three types of stigma on HRQoL but the mediating effect of HIV symptom management self-efficacy was only found in the pathway between anticipated stigma and HRQoL.

Conclusions: This dissertation provided support for the different psycho-behavioral mechanisms of HIV-related stigma on clinical outcomes. Future stigma research should consider the characteristics of each type of HIV-related stigma and clinical outcomes and use the relevant theoretical knowledge to frame the pathways between them. Interventions aiming to improve clinical outcomes should be tailored to internalized, anticipated, and enacted stigma, target relevant psycho-behavioral pathways, and promote the resilience of PLWH.

Keywords: Adherence, China, Clinical outcomes, HIV, Self-efficacy, Stigma

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AACTG .... Adult AIDS Clinical Trials Group

AIC .... Akaike Information Criterion

AICC .... Corrected Akaike Information Criterion

AIDS .... Acquired Immune Deficiency Syndrome

ANOVA .... Analysis of Variance

AOR .... Adjusted Odds Ratio

ART .... Antiretroviral Therapy

BIC .... Bayes Information Criterion

BMI .... Body Mass Index

CDC .... Center for Disease Control and Prevention

CES-D .... Center for Epidemiologic Studies-Depression

CFI .... Comparative Fit Index

CI .... Confidence Interval

FIML .... Full Information Maximum Likelihood Estimation

HIV .... Human Immunodeficiency Virus

HRQoL .... Health-related Quality of Life

LGCM .... Latent Growth Curve Model

MAR .... Missing at Random

MCAR .... Missing Completely at Random

MLR .... Robust Maximum Likelihood Estimation

MOS-HIV .... Medical Outcomes Study HIV Health Survey

OR .... Odds Ratio

PLWH .... People Living with HIV

QIC .... Queensland Investment Corporation

RMSEA .... Root Mean Square Error of Approximation

SD .... Standard Deviation

SE .... Standard Error

SEAMS .... Self-efficacy for Appropriate Medication Use Scale

SES .... Socioeconomic Status

SRMR .... Standardized Root Mean Residual

UNAIDS .... Joint United Nations Programme on HIV/AIDS

VIF .... Variance of Inflation

CHAPTER 1

INTRODUCTION

1.1 General introduction to HIV epidemic

The global efforts to control and prevent Human Immunodeficiency Virus (HIV) have significantly reduced its morbidity and mortality since 2010 (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2020a, 2020b), but the current global HIV epidemic is still a critical public health challenge. By the end of 2019, it is estimated that there were about 38 million people living with HIV (PLWH) and 690,000 Acquired Immune Deficiency Syndrome (AIDS) related deaths worldwide (UNAIDS, 2020a). Nearly 80% of PLWH and 90% of the AIDS-related deaths were found in sub-Saharan Africa and Asia and the Pacific areas (UNAIDS, 2020b).

To control HIV-related morbidity and mortality, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the “90-90-90” and “95-95-95” goals in 2014 (Lima et al., 2017; Marsh et al., 2019). These goals are by 2020 and 2030, respectively, (1) at least 90% and 95% of all PLWH will know their HIV status; (2) at least 90% and 95% of the confirmed cases will receive antiretroviral therapy (ART); and (3) at least 90% and 95% of the PLWH on ART will achieve viral suppression (Lima et al., 2017; Marsh et al., 2019). However, the current progress on HIV prevention around the world still does not meet these goals (Marsh et al., 2019). Among the 38 million

PLWH worldwide, only 62% are currently on ART and 53% had achieved viral suppression in 2018 (Marsh et al., 2019).

China has undertaken large efforts on HIV control and prevention, such as "Four Frees and Once Care" policy to promote HIV treatment and care, infrastructure development on surveillance and case management, and regular monitoring of treatment failure and drug resistance. However, the nation still has large number of PLWH (Wu, Chen, Scott, & McGoogan, 2019; Wu, McGoogan, & Detels, 2021). The total numbers of PLWH in China have steadily increased since 2005, and there were more than 1.25 million cumulative cases (diagnosed and undiagnosed cases) by the end of 2018, with nearly 80,000 new cases diagnosed during the same year (Wu et al., 2021). The distribution of PLWH varies significantly in China with clusters in the southwestern provinces and resource-limited areas, such as Yunnan, Sichuan, and Guangxi (Wu et al., 2019; Wu et al., 2021). Guangxi, an autonomous region in southwestern China, consistently ranked third in the number of HIV case among the 31 provinces in China from 2014 to 2018 (Wu et al., 2019).

Although there was remarkable achievement in HIV control and prevention, the progresses on the UNAIDS' "90-90-90" and "95-95-95" goals are still unsatisfactory in China. For example, in 2018, the ART coverage rate among PLWH was 83%, and 94% of them achieved viral suppression (Wu, 2019). Substantial variation of viral suppression was identified in different areas, especially in the rural provinces and resource-limited areas, such as Guangxi (Zhao, Han, Ma, & Li, 2019). Using large representative samples of PLWH in Guangxi, a previous study found that in 2017, only 77.3% of the PLWH were on ART and 82.5% of them were virally suppressed (Yang et al., 2019). The failure to meet UNAIDS' goals indicates that more research investigating the barriers and facilitators of optimal clinical outcomes are needed, which could inform future clinical efforts to reduce treatment failure, improve the health of PLWH, and limit new cases of HIV.

1.2 Clinical outcomes among PLWH

Clinical outcomes in this dissertation were CD4 count, viral suppression, and health-related quality of life (HRQoL). CD4 count and viral load are important indicators of successful ART (Andersson et al., 2020; Limmade, Fransisca, Rodriguez-Fernandez, Bangs, & Rothe, 2019). CD4 count, the total numbers of CD4 T-cells in body, represents the immunologic functioning and ability to fight with infections (Center for Disease Control and Prevention [CDC], 2019). Viral load, the amount of HIV virus in the body, is an indicator of infection stage (i.e., acute HIV infection, chronic HIV infection, AIDS) among PLWH (CDC, 2019). CD4 count and viral load are closely correlated with each other across the three infection stages. At the beginning of infection (first 10 days or so), the HIV will attack CD4 cells and use them inside the lymph nodes to reproduce and replicate. During the next few weeks (two weeks or more), the viral load increases to high levels (higher than 10 million copies/ml), and nearly 80% ~ 90% of the total CD4 cells will be killed by the virus (i-base, 2019). Then, the immune system fights back and produces antibodies to HIV. During this period (nearly six months), the viral load drops to lower levels, and CD4 count will recover. During this time, it is estimated that nearly 70% of the PLWH have symptoms, such as fevers and fatigue (i-base, 2019). After the acute infection stage and without treatment, HIV enters the chronic infection stage, which often progresses slowly. As time increases, the CD4 count will steadily drop and viral load will steadily increase. At any infection stages, the initiation of ART can slow disease progression, recover immunologic functioning, and reduce the chance to develop opportunistic infections (Fogarty et al., 2002; Nieuwkerk & Oort, 2005; Press, Tyndall, Wood, Hogg, & Montaner, 2002). A few days after ART initiation, about 90% of the virus will be killed, and the viral load become undetectable within one to three months (i-base, 2019). However, the CD4 count increases slowly, especially for those with low CD4 count at the beginning of ART. The normal CD4 range for HIV negative population is between 500 and 1,600, with higher levels of CD4 count indicating better immunologic functioning (i-base, 2019).

HRQoL is the third important indicator of successful ART. PLWH with considerable levels of CD4 count and viral suppression still need to contend with other challenges, such as potential side effects of ART, the possibility of treatment failure, and other comorbidities. Thus, HRQoL is the individual's perceived quality of daily life (CDC, 2018) and thus could be an important construct for PLWH under care (Andersson et al., 2020; Lazarus et al., 2016; Webster, 2019). It reflects the disease burden across four main dimensions (i.e., physical health, psychological health, social functioning, perception about general health) and provides a comprehensive measure of overall health quality among PLWH (Ashing-Giwa, 2005; Ruiz Perez et al., 2005; Wu, Hays, Kelly, Malitz, & Bozzette, 1997).

HIV infection could compromise PLWH's HRQoL in terms of multiple dimensions. First, physical health is of critical importance for PLWH. If PLWH are unable to achieve viral suppression, they are at risk for deadly opportunistic infections and rapid disease progression—ultimately culminating in AIDS and death (Gesesew, Ward, Woldemichael, & Mwanri, 2018). Second, in the face of stressful events and adversities, PLWH have high risks for mental health problems (e.g., depression and perceived stress) and poor psychological well-being (Kidia, Ndhlovu, Jombo, Abas, & Makadzange, 2015; Zeng et al., 2018). Third, being stigmatized and discriminated by others may harm the social functioning of PLWH, including by causing challenges to interpersonal relationships and limited opportunities to give and receive social support from others (Earnshaw & Chaudoir, 2009; Turan et al., 2019; Turan et al., 2016). Finally, given all these challenges, PLWH may have negative perceptions about their general health.

Prior research identifies a number of psychosocial factors that may affect clinical outcomes (i.e., CD4 count, viral load, HRQoL) among PLWH including but not limited to stress stimuli or stressors (e.g., HIV-related stigma, daily stress) (Bhat et al., 2015; Darlington & Hutson, 2017), psychological distress (e.g., depression, anxiety, perceived stress) (Ajose, Mookerjee, Mills, Boulle, & Ford, 2012; Gore-Felton & Koopman, 2008; Pence, 2009), coping strategies (e.g., avoid coping, denial coping) (Bhat et al., 2015), and behavioral health problems (e.g., substance use, alcohol use) (Ajose et al., 2012; Gore-Felton & Koopman, 2008; Pence, 2009; Sheehan et al., 2020). Among these factors, HIV-related stigma, as a chronic stressor for PLWH, is a well-established factor undermining clinical outcomes. Based on the Health Stigma Framework and empirical evidences, HIV-related stigma included internalized, anticipated, and enacted stigma, which may influence clinical outcomes through psycho-behavioral mechanisms (Earnshaw & Chaudoir, 2009; Earnshaw, Smith, Chaudoir, Amico, & Copenhaver, 2013). The investigation on these potentially distinct mechanisms could inform tailored interventions on the mediators in the pathways and alleviate the negative impacts of HIV-related stigma.

1.3 HIV-related stigma and its impacts on health outcomes

HIV-related stigma is one of the well-established barriers to good mental and physical health of PLWH. Stigma can be defined as a “discrediting and tainting social label”, and it has been found to inhibit health-seeking behaviors, timely diagnosis, prevention efforts, and linkage to treatment and care (Alonzo & Reynolds, 1995; Andersson et al., 2020; Goffman, 1963). According to the Health Stigma Framework (Figure 1.1), being diagnosed with HIV, PLWH may experience *internalized, anticipated,* and *enacted stigma* when they perceive prejudice, stereotypes, and discrimination from others (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013).

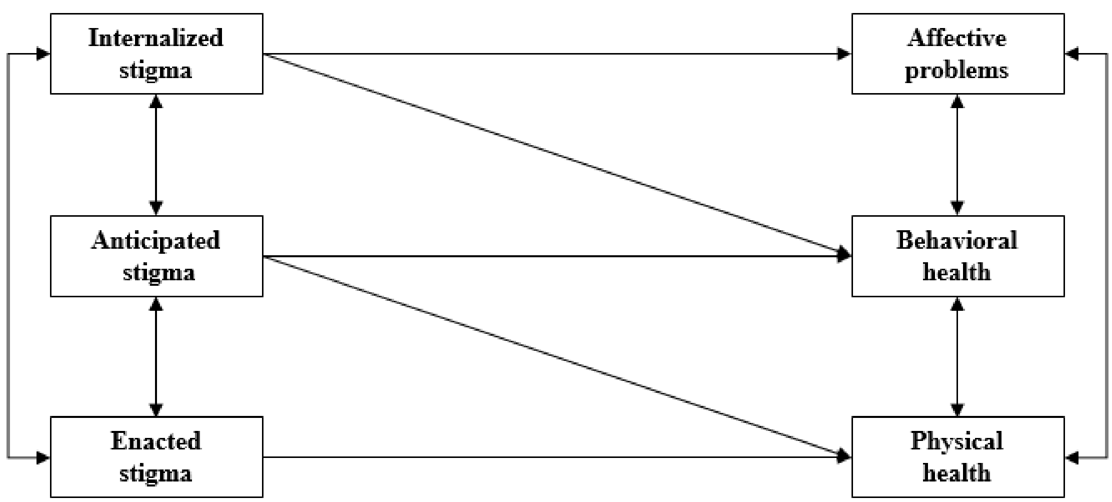

Figure 1.1 Health stigma framework (Earnshaw et al., 2013)

The three types of HIV-related stigma reflect the cognitions, beliefs, and experiences of discrimination against PLWH because of HIV (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013; Quinn & Earnshaw, 2011). *Internalized stigma* represents the cognitions of being discriminated by others among PLWH because of their HIV positive status. Indeed, it refers to the cognitive process of believing that the negative attributes associated with HIV are true of the self (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013). PLWH with high levels of internalized stigma would apply these negative beliefs to themselves and believe that they are devalued or bad as compared to others (Quinn & Earnshaw, 2011; Sayles, Wong, Kinsler, Martins, & Cunningham, 2009). *Anticipated stigma* is the perception of PLWH believing that they may experience discrimination if others know their HIV status (Quinn & Earnshaw, 2011). It could directly capture PLWH's fears of being discriminated if they disclose their HIV status to others. *Enacted stigma* is PLWH's actual experience of being discriminated by others (Quinn & Earnshaw, 2011). When HIV status is known either through voluntary disclosure, unintended disclosure, or through information passed from one to others, PLWH may be treated by others in stigmatizing ways.

Internalized, anticipated, and enacted stigma are closely associated with psychological wellbeing among PLWH. Particularly, previous studies focused on the close relationship between internalized stigma and psychological wellbeing, such as depression (Chi, Li, Zhao, & Zhao, 2014; Zeng et al., 2018), stress (Guo et al., 2020; Zhu et al., 2020), and self-efficacy (Zeng et al., 2020; Zhou, Li, Qiao, Shen, & Zhou, 2020). Additionally, people (e.g., PLWH, sexual minorities) who anticipated greater stigma and/or had experience of being stigmatized are more likely to experience greater psychological distress (Quinn & Chaudoir, 2009), low self-esteem (Berger, Ferrans, & Lashley, 2001), and other mental health problems.

In addition to psychological wellbeing, the three types of stigma have strong associations with behavioral health, such as ART adherence (Sweeney & Vanable, 2016), healthcare utilization (Chesney & Smith, 1999), disclosure (Rongkavilit et al., 2010), and risk behaviors (Elkington et al., 2010). Particularly, internalized, anticipated, and enacted stigma are closely associated with ART adherence among PLWH (Camacho, Kalichman, & Katner, 2020; Sweeney & Vanable, 2016; Zeng et al., 2020). PLWH with high levels of internalized stigma may believe that they are devalued and not deserved to the treatment (Quinn & Earnshaw, 2011). Additionally, they may have more negative attitudes towards the treatment and lower recovery orientations (Ritsher, Otilingam, & Grajales, 2003). Anticipated and enacted stigma may increase PLWH's concerns in healthcare settings, which in turn may impede them from utilizing healthcare resources and adhering to medications (Peitzmeier, Grosso, Bowes, Ceesay, & Baral, 2015; Peltzer & Ramlagan, 2011; Zeng et al., 2020).

Even though less studied than psychological wellbeing and behavioral health, stigma has been found to directly and indirectly undermine the physical wellbeing among people with stigmatized identities, such as PLWH, drug users, and sexual minorities. For instance, internalized stigma among PLWH (Wolitski, Pals, Kidder, Courtenay-Quirk, & Holtgrave, 2009) and enacted stigma in drug users (Ahern, Stuber, & Galea, 2007) are associated with decreased overall physical health. An existing study also found that anticipated and enacted stigma among HIV positive gay men could act as stressors and accelerate their HIV progression, such as times to a critically low level of CD4 count (15% of total peripheral blood lymphocytes), time to AIDS diagnosis, and time to HIV-related mortality (Cole, Kemeny, & Taylor, 1997). Additionally, the three types of stigma may influence physical wellbeing through the aforementioned psycho-behavioral mechanisms, such as self-efficacy (Zeng et al., 2020; Zhou et al., 2020), ART adherence (Sweeney & Vanable, 2016), and healthcare utilization (Chesney & Smith, 1999).

1.4 Preview

This dissertation consists of six chapters and aims to investigate the impacts and mechanisms of HIV-related stigma on clinical outcomes among PLWH in Guangxi, China. Chapter 1 introduces the HIV epidemic around the world, clinical outcomes, and HIV-related stigma. Chapter 2 presents a review of existing literature about clinical outcomes and HIV-related stigma, literature gaps, research questions, conceptual framework, research aims and hypotheses, and significance. Chapter 3 gives detailed introduction to the methodology. Chapters 4 and 5 summarize the findings in the form of two studies. Chapter 6 provides an overall discussion of the research findings, strengths and limitations, implications, and future direction.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

2.1 Introduction to clinical outcomes among PLWH in China

Viral load and CD4 count are critical clinical indicators for determining the clinical stages of HIV infection, evaluating the efficacy of treatment, and changing treatment regimens when necessary. With widespread application of ART in 1990s and others efforts on promoting ART, although the ART coverage and viral suppression rates have increased among PLWH in China, the overall progress still does not achieve the "90-90-90" and "95-95-95" goals set by UNAIDS (Wu, 2019). By the end of 2015, only 67% of the diagnosed PLWH were receiving ART, and 65% of them were virally suppressed (Ma et al., 2018; Wu, 2016). The ART coverage rate among PLWH increased by 16%, and the viral suppression increased by 29% (Wu, 2019; Zhao et al., 2019) from 2015 to 2018. Spatial variation in viral suppression persists across different provinces of China. For instance, in Guangdong province, a study found that the viral suppression rate among PLWH was 93.3% after ART initiation (Huang et al., 2015). In Yunnan, a southwestern province, Chen and colleagues (Chen et al., 2014) found that 81.3% of the PLWH on ART reached viral suppression. In terms of CD4 count, an important indicator of immunologic functioning, a nationwide retrospective cohort study found that nearly 80% of the PLWH who initiated ART had their CD4 counts between 200 ~ 349 cells/μl

(Hu et al., 2017), which were still not within the typical range for a healthy immune system (CD4 count ≥ 500 cells/μl).

HRQoL is a comprehensive construct of health and disease burden. Due to HIV, PLWH may experience lower levels of HRQoL than the general population (Lan et al., 2015). For example, Lan and colleagues (2015) found that using the 36-item Short Form Health Survey health survey, the average score of HRQoL among PLWH was 64.7, which was significantly lower than that of the general population (64.7 vs. 78.2, $p < 0.001$). Particularly, PLWH had much lower scores in their perception about general health (48.3 vs. 66.0, $p < 0.001$) and social functioning (44.6 vs. 84.6, $p < 0.001$) than the HIV-negative population (Lan et al., 2015). In terms of geographic disparities in HRQoL among Chinese individuals, PLWH from urban areas (e.g., Beijing) have been found to have higher levels of HRQoL than those in rural areas or resource-limited settings (e.g., Jiangxi) (Lan et al., 2016; Rao et al., 2012). Extant research has also documented age, gender, and socioeconomic status (SES) disparities in HRQoL among PLWH (Lan et al., 2015; Lan et al., 2016; Xiao, Lin, Li, & Ji, 2019). Indeed, male PLWH reported higher levels of HRQoL than female (Xiao et al., 2019). Age is negatively associated with HRQoL while SES has positive impact on HRQoL (Lan et al., 2015; Lan et al., 2016; Xiao et al., 2019).

As one of the regions with high burden of HIV epidemic in China, Guangxi had over 86,000 PLWH, ranking third in the terms of the number of HIV cases among the 31 provinces in China in 2018 (Guangxi Center for Disease Control and Prevention [CDC], 2018; Wu et al., 2019). With the scaling up of ART, there were increased trends of ART coverage (from 72.1 to 91.2%) and CD4 count (from 318 to 357 cells/μl) among PLWH in Guangxi (Chen et al., 2019; Yang et al., 2019) from 2012 to 2017. However, rates of viral suppression did not show a similar trend of improvement (Yang et al., 2019). The challenges of viral suppression include but are not limited to low levels of ART knowledge and treatment interruptions among PLWH in Guangxi. Besides, nearly half of the PLWH in Guangxi had their CD4 count less than 350 cells/μl. Furthermore, although the initiation of ART could significantly improve the overall HRQoL among PLWH in Guangxi, China at the first 6-month, the effect size decreased after 12-month (Ming et al., 2014). In sum, the suboptimal outcomes of viral suppression, CD4 count, and HRQoL among PLWH on ART in Guangxi implies that more research is needed to investigate their correlates and how various factors influence them.

2.2 HIV-related stigma in China

PLWH in China suffer from serious HIV-related stigma. The two key characteristics, including collectivism and family responsibilities, of Chinese culture may cultivate HIV-related stigma against PLWH in China (Liu et al., 2006). The collectivist culture subordinates individual interests to those of the group and requires people in the same group to maintain dignity, respect, and social status in the social structure (Hui & Triandis, 1986; Kleinman et al., 1995; Murray-Johnson et al., 2001; Triandis, Bontempo, & Villareal, 1988). People may be devalued or condemned if they do not comply with the rules in collectivist culture. As HIV infection is closely related to stigmatizing behaviors, such as commercial sex, casual sex, and injection drug use, PLWH may be devalued by the collectivist society as the collective value is considered to be destroyed by these individuals (Liu et al., 2006). What is more, the Chinese culture emphasizes family responsibilities, such as maintaining and protecting family (males' responsibilities) and taking care of the home, the children, and the rest of the family (females' responsibilities). Because of HIV, PLWH who do not have access to ART may suffer from serious health burden and may not fully take on family responsibilities. Particularly, some PLWH who are sexual minorities may not have children to maintain the family bloodline, which may put them at risk for stigma (Li, Holroyd, Lau, & Li, 2015).

PLWH in Guangxi are vulnerable to HIV-related stigma. Guangxi is one of the resource-limited provinces and located in the southern China. Therefore, compared with other developed provinces with relatively sufficient resources, Guangxi is more conservative in regard to the Chinese culture. Additionally, the HIV epidemic in Guangxi could be characterized as a rural phenomenon with many PLWH being rural residents, from low socioeconomic status (SES), and being infected mostly through sexual contact (Wang, 2013; Yang et al., 2019). Hence, due to the conservative culture, limited knowledge of HIV infection, and local HIV epidemic, PLWH in Guangxi may experience high levels of HIV-related stigma.

2.3 Impacts of HIV-related stigma on clinical outcomes

HIV-related stigma is one of the major barriers to viral suppression, immunologic functioning, and HRQoL. Extant literature found that higher levels of HIV-related stigma were associated with higher risks of detectable viral load (Berger et al., 2001; Kemp et al., 2019; Lipira et al., 2019; Prati et al., 2015; Umar et al., 2019) and lower CD4 count (Peltzer & Ramlagan, 2011; Walburn, Swindells, Fisher, High, & Islam, 2012). For instance, Umar and colleagues (2019) found that among the 209 youths living with HIV in Malawi, HIV-related stigma was positively related to detectable viral load after adjusting for key sociodemographic characteristics. Using a qualitative research design, Walburn and colleagues (2012) found that HIV-related stigma negatively affected the engagement in care and resulted in a drop in CD4 count.

HIV-related stigma could compromise PLWH's HRQoL through its impacts on the four dimensions (i.e., psychological health, physical health, social functioning, perception about general health). First, HIV-related stigma, as a chronic stressor, puts PLWH at risks of psychological distress (e.g., perceived stress, depression, anxiety) and compromises their mental health (Abdul Bari, 2017; Alsayed, Sereika, Albrecht, Terry, & Erlen, 2017; Song, Yan, Lin, Wang, & Wang, 2016). Second, PLWH with higher levels of HIV-related stigma may be less likely to engage/retain in care and adhere to ART, which in turn could impair their immunologic functioning, increase viral load, and compromise their physical health (Abdul Bari, 2017; Alsayed et al., 2017). Third, due to HIV-related stigma, PLWH may have fewer or poorer quality interpersonal relationships, less social interaction, fewer and smaller social networks, less opportunity to give and receive social support, and fewer resources to cope with their psychological distress and to support them in their HIV care and ART adherence (Abdul Bari, 2017; Song et al., 2016; Turan, Hatcher, et al., 2017). The negative influences of HIV-related stigma on mental health, physical health, and social functioning may prevent PLWH from having positive perceptions about their general health and thus result in low levels of HRQoL (Abdul Bari, 2017).

For the relationships between different types of HIV-related stigma and clinical outcomes, there were few research considering internalized, anticipated, and enacted stigma at the same time and testing the separate impacts of them on the outcomes. In fact, these impacts may be different by different types of HIV-related stigma (Kemp et al., 2019; Prati et al., 2015). The research findings were inconsistent. For instance, Prati and colleagues (2015) found that viral suppression was significantly associated with internalized stigma but not with enacted stigma while Kemp and colleagues (2019) found the inverse. In regard to HRQoL, Fuster-Ruizdeapodaca and colleagues (2014) investigated the impacts of enacted and internalized stigma and found that only enacted stigma had direct effect on HRQoL among PLWH. However, an existing study among men living with HIV in Tanzania found the inverse pattern (Parcesepe et al., 2020).

2.4 Mechanisms of HIV-related stigma and clinical outcomes

Researchers have conceptualized the mechanisms through which HIV-related stigma may result in poor virologic and immunologic outcomes (Earnshaw & Chaudoir, 2009; Turan, Hatcher, et al., 2017). Particularly, the various types of HIV-related stigma (i.e., internalized, anticipated, enacted stigma) may influence these outcomes through four main pathways including interpersonal factors (e.g., social support, social isolation), psychological distress (e.g., depression, anxiety, perceived stress), behavioral factors (e.g., care engagement, ART adherence, disclosure), and resource access (e.g., treatment-related skills, knowledge, resources for coping with stressors) (Earnshaw & Chaudoir, 2009; Turan, Hatcher, et al., 2017). Psychological distress (i.e., depression) and behavioral factors (i.e., ART adherence) are well-investigated mediators between HIV-related stigma and virologic and immunologic outcomes although findings were inconsistent (Katz et al., 2013; Lipira et al., 2019; Logie et al., 2019). For example, depressive symptoms and ART adherence could mediate the relationship between overall HIV-related stigma and CD4 count (Logie et al., 2019). However, such mediating effects were found between overall measures of HIV-related stigma and viral suppression (Lipira et al., 2019).

Although prior research conceptualized and investigated the underlying mechanisms of HIV-related stigma on HRQoL, most studies focused on the mediating effects of psychological distress (e.g., depression) (Alsayed et al., 2017; Li et al., 2015; Relf et al., 2019; Shrestha et al., 2017) and social functioning (e.g., social support) (Logie, Ahmed, Tharao, & Loutfy, 2017; Logie et al., 2018; Rao et al., 2012). Research exploring how HIV-related stigma influences HRQoL through its negative impacts on the mediators relevant to physical health is needed. For instance, Zhou and colleagues (2020) found that HIV symptom management self-efficacy mediated the relationship between internalized stigma and HRQoL among PLWH in Guangxi, China. The possible reason might be that HIV symptom management self-efficacy is closely related to the symptom management behaviors (e.g., keeping symptoms from interfering with social functions, adhering to medical appointment, controlling medication-induced side effects) which may influence the physical health of PLWH.

In regard to the mechanisms through which different types of HIV-related stigma may impact clinical outcomes, empirical evidence is still limited. Even though Earnshaw and colleagues (2013) tested the separate effects of internalized, anticipated, and enacted stigma on CD4 count based on Health Stigma Framework, they did not elaborate on the mechanisms underlying them. Additionally, there is a dearth of research examining the potentially distinct mechanisms of internalized, anticipated, and enacted stigma on HRQoL among PLWH, which could inform targeted interventions to mitigate the negative impacts of different types of HIV-related stigma on overall health quality.

In sum, the well-investigated mechanisms of HIV-related stigma on clinical outcomes were psycho-behavioral mediators, especially psychological distress. However, these studies ignored the importance of psychological resources, such as treatment-related self-efficacy (Turan, Hatcher, et al., 2017). Psychological resources refer to the tools, skills, confidences, and motivations that PLWH use to cope with stressful events, keep daily routine, and maintain their health, and they are important mechanisms underlying HIV-related stigma and clinical outcomes (Turan, Hatcher, et al., 2017). HIV-related stigma may cause PLWH to believe that they are less capable and confident in dealing with treatment-related issues (i.e., medical visits, adherence behaviors), which may result in low self-efficacy related to ART adherence and suboptimal clinical outcomes (Seghatol-Eslami et al., 2017). For instance, using cross-sectional data, Zeng and colleagues found a significant indirect effect from anticipated stigma to ART adherence through ART self-efficacy (Zeng et al., 2020). However, limited studies investigated the mechanisms of HIV-related stigma on clinical outcomes through psychological resources from a longitudinal perspective. Research exploring the mediating roles of psychological resources in the pathways from HIV-related stigma to clinical outcomes could inform future interventions to buffer stigma's negative impacts, promote treatment-related behaviors, and improve clinical outcomes.

2.5 Literature gaps

Based on the literature review, some research gaps need to be acknowledged. First, most existing studies examined the bivariate relationships between HIV-related stigma and clinical outcomes, and few studies elucidated the pathways between them (Alsayed et al., 2017; Kemp et al., 2019; Rangarajan et al., 2016; Sumari-de Boer, Sprangers, Prins, & Nieuwkerk, 2012). Second, among the studies investigating how stigma influenced clinical outcomes, many of them focused on the mediating effect of psychological distress but ignored the importance of psychological resources, especially the treatment-related self-efficacy (Lipira et al., 2019; Logie et al., 2019; Turan et al., 2019). The most well-investigated mediator pertinent to treatment was adherence behaviors (Lipira et al., 2019; Logie et al., 2019), and studies exploring other treatment-related pathways are needed among PLWH. Third, most studies investigating the mechanism of HIV-related stigma on clinical outcomes used cross-sectional design (Turan et al., 2019). Therefore, they did not have sufficient ability to confirm the causality. Fourth, although there were some studies exploring the mechanisms underlying stigma and health outcomes, most of them employed traditional path analysis and examined the associations among variables of interest (Turan et al., 2019). The traditional path analysis did not test the associations among the changes of key variables and thus could not confirm whether the change of independent variable leads to the change of outcome (Cheong, Mackinnon, & Khoo, 2003). Fifth, previous studies predominantly focused on the overall measure of HIV-related stigma or one or more types (i.e., internalized, anticipated, enacted stigma) without considering all three types of stigma simultaneously and examining their separate impacts or mechanisms on clinical outcomes (Fuster-Ruizdeapodaca, Molero, Holgado, & Mayordomo, 2014; Logie et al., 2019; Parcesepe et al., 2020). Finally, current research regarding the relationships between HIV-related stigma and clinical outcomes concentrated in Africa (e.g., Malawi and Tanzania) (Parcesepe et al., 2020; Umar et al., 2019), United States (Kemp et al., 2019), or European (Prati et al., 2015). However, limited studies have been conducted in other resource-limited settings with conservative culture, a large HIV population, and high levels of HIV-related stigma against PLWH, such as Guangxi, China.

2.6 Conceptual framework

To address these knowledge gaps, this dissertation developed a conceptual framework (Figure 2.1) based on the Health Stigma Framework and extant research. In this conceptual framework, clinical outcomes including CD4 count, viral suppression, and HRQoL were the primary outcomes. This dissertation tested the ART specific psycho-behavioral pathways between three types of HIV-related stigma and each clinical outcome. ART adherence was the behavioral mediator examined in this dissertation, as currently it is the most well-investigated mechanism of HIV-related stigma on clinical outcomes (Lipira et al., 2019; Logie et al., 2019; Sweeney & Vanable, 2016). However, most of the previous studies used cross-sectional design, and their findings were inconsistent. Self-efficacy, a key psychological resource for behavioral change, may influence clinical outcomes through improving PLWH's confidence on adherence behaviors (Zeng et al., 2020) and HIV symptom management (e.g., keeping symptoms from interfering with social functions, adhering to medical appointment, controlling medication-induced side effects) (Zhou et al., 2020). Thus, ART self-efficacy and HIV symptom management self-efficacy were two main psychological mechanisms examined in this dissertation.

Internalized, anticipated, and enacted stigma may influence clinical outcomes through psycho-behavioral mechanisms (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013; Turan, Hatcher, et al., 2017). Extant research found that the high levels of HIV-related stigma reduced self-efficacy (Zeng et al., 2020; Zhou et al., 2020), the motivation and confidence for behavioral change. The low motivation and confidence in behavioral change resulted in the suboptimal adherence behaviors (Zeng et al., 2020) and symptom management (Zhou et al., 2020), which in turn impaired the clinical outcomes among PLWH on ART. Therefore, the three types of HIV-related stigma were the barriers of optimal clinical outcomes through reducing self-efficacy for ART and symptom management and ART adherence. Finally, based on extant findings, all three types of HIV-related stigma were assumed to have direct impacts on the clinical outcomes.

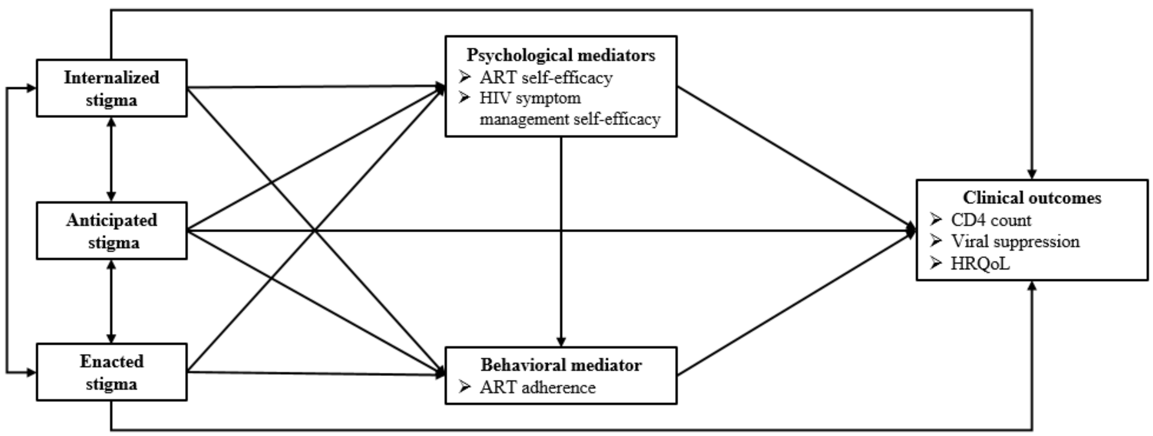

Figure 2.1 Conceptual framework

2.7 Research aims

This dissertation addressed the knowledge gaps based on two specific aims and in a form of two studies. The specific aims were carried out using data derived from a prospective cohort study among PLWH in Guangxi, China. Chapter 3 gives detailed description on the design of cohort study and data analysis. The specific aims in this dissertation are:

Aim 1. To examine the longitudinal impacts of internalized, anticipated, and enacted stigma on clinical outcomes among PLWH. Aim 1 examined the separate relationships between three types of HIV-related stigma on each clinical outcome (i.e., CD4 count, viral suppression, HRQoL) after adjusting for psycho-behavioral factors and sociodemographic characteristics.

According to the Health Stigma Framework (Figure 1.1), empirical evidences, and conceptual framework of this dissertation (Figure 2.1), the hypotheses for aim 1 were

Hypothesis 1a: The three types of HIV-related stigma could explain additional variances in clinical outcomes after controlling for psycho-behavioral factors and other covariates.

Hypothesis 1b: Internalized, anticipated, and enacted stigma would have significant and negative impacts on the three clinical outcomes. High levels in these three types of HIV-related stigma would result in suboptimal clinical outcomes.

Aim 2. To elucidate the longitudinal mechanisms of internalized, anticipated, and enacted stigma on clinical outcomes through psycho-behavioral pathways. In aim 2, this dissertation incorporated the three types of HIV-related stigma into the same model and examined the pathways from them to each clinical outcome via psycho-behavioral mediators.

Based on the Health Stigma Framework (Figure 1.1), empirical evidences, and conceptual framework of this dissertation (Figure 2.1), the hypotheses for aim 2 were:

Hypothesis 2a: The direct impacts of internalized, anticipated, and enacted stigma on the three clinical outcomes were significant and negative.

Hypothesis 2b: All three types of HIV-related stigma could influence each clinical outcome through the mediating effects of psycho-behavioral factors. Particularly, the serial mediating effect from HIV-related stigma, treatment-related self-efficacy, ART adherence, and clinical outcome would be significant.

2.8 Significances

2.8a Importance of clinical outcomes

CD4 count, viral load, and HRQoL are critical indicators for evaluating the effectiveness of ART regimens and making further clinical decisions among PLWH under HIV treatment and care. CD4 count reflects the immunologic functioning, and viral suppression is the primary measure of treatment-efficacy (Limmade et al., 2019). PLWH with ample CD4 count and undetectable viral load have good immunologic functioning, slow their disease progression, and have their life expectancy improved (Fogarty et al., 2002; Nieuwkerk & Oort, 2005; Press et al., 2002). Additionally, undetectable viral load in PLWH eliminates the risk of HIV transmission and is thus a key component of efforts to end the HIV epidemic. Compared with CD4 count and viral load, HRQoL encompasses four main dimensions (i.e., psychological health, physical health, social functioning, perception about general health) and gives a comprehensive assessment of health among PLWH (Lazarus et al., 2016; Webster, 2019). Therefore, HRQoL is a goal beyond immunologic recovery and viral suppression among PLWH on ART, and it has been considered as a "fourth 90" goal for ending HIV epidemic (Lazarus et al., 2016). Higher levels of HRQoL could ensure PLWH to have better physical and psychological wellbeing, lower risk of developing comorbidities and positive perception about their general health.

2.8b Impacts and mechanisms of HIV-related stigma on clinical outcomes

Given a large number of extant research that has only investigated the impacts and mechanisms of overall HIV-related stigma on health outcomes, this dissertation is of public health significance by distinguishing the separate impacts and mechanisms of internalized, anticipated, and enacted stigma. First, based on the Health Stigma Framework (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013) and empirical evidence, internalized, anticipated, and enacted stigma may have differential impacts on psychological, behavioral, and physical wellbeing. However, limited studies conducted these investigation. The investigation on these potentially distinct associations could inform targeting specific type of HIV-related stigma and improving specific health outcomes. For example, Guo and colleagues (2020) found that interventions targeting internalized stigma could significantly reduce the depressive symptoms among PLWH in Guangzhou, China. Second, uncovering the mechanisms of internalized, anticipated, and enacted stigma on health outcomes through psycho-behavioral pathways could inform future stigma reduction interventions to target specific mediator in order to alleviate the negative impact of stigma. For instance, as depression could mediate the relationship between internalized stigma and suicidal behaviors (Zeng et al., 2018), interventions targeting both internalized stigma and depression may reduce the risk of suicide among PLWH effectively. Finally, although the bivariate association between overall measure of stigma and viral load had been verified in previous studies (Kemp et al., 2019; Lipira et al., 2019), the underlying mechanisms between them are still unclear. This dissertation could help to disentangle various types of stigma in order to uncover these mechanisms, which could inform future efforts that improve clinical outcomes and the physical health and mental health of PLWH.

2.8c Vulnerability of PLWH in Guangxi, China

The traditional sociocultural context of China and resource-limited setting in Guangxi make PLWH vulnerable to HIV-related stigma and suboptimal clinical outcomes. Most of HIV cases in Guangxi are attributable to HIV-related risk behaviors (e.g., unprotected sexual behaviors with multiple or same-sex partners, injection drug use) that are traditionally not socially accepted in Chinese culture (Herek, 2016; Liu et al., 2006), especially the conservative Chinese culture in Guangxi. Additionally, some HIV-related risk behaviors (e.g., sex work, injection drug use) are illegal in China, and PLWH with history of these risk behaviors would be punished and socially disapproved of, which may further exacerbate their HIV-related stigma (Liu et al., 2006). Guangxi, a rural province in southwestern China, has a large rural population. The HIV epidemic in Guangxi could be characterized as a rural phenomenon as many PLWH are rural residents, from low SES, and acquire HIV primarily through sexual activity (Wang, 2013). Hence, in addition to HIV-related stigma, the resource-poor setting, low SES, and limited knowledge of HIV infection set barriers between PLWH in Guangxi and healthcare resources and HIV treatment.

CHAPTER 3

METHODOLOGY

3.1 Overview of cohort study

Data used in this dissertation were derived from a prospective cohort study among 1,198 PLWH in Guangxi, China, which was funded by the National Institute of Health/National Institute of Mental Health (Grant No. RO1MH0112376). This cohort study aims to investigate the mechanisms underlying HIV-related stigma and clinical outcomes among PLWH. With the assistance and collaboration of Guangxi Center for Disease Control and Prevention (Guangxi CDC), six major public hospitals/clinics in five cities with the largest number of HIV patients under care were selected as the study sites. The volume of HIV patients at each study site ranged from 1,386 to 7,389 at the time of baseline survey. A systematic sampling approach was employed to randomly select the participants from all eligible PLWH. Specifically, the medical staff or case managers in each site used an arbitrary number (e.g., the date of the month) to identify the first case to be sampled from the eligible patient pool, and then every n^{th} case was selected where n is a pre-calculated interval for each sampling iteration (e.g., ratio of target sample size to the total numbers of patients in the pool). The process was repeated until the target sample size was achieved at each clinic.

3.2 Participants

PLWH who fulfilled the eligibility were invited to participate in the cohort study. The inclusion criteria of PLWH were PLWH who: (1) were aged between 18 and 60 years old, (2) had a confirmed diagnosis of HIV, and (3) had no plan to permanently relocate outside of the Guangxi province in the next 12 months. The exclusion criteria were: (1) mental and physical inability to respond to assessment questions, and (2) currently incarcerated or institutionalized for drug use or commercial sex. PLWH who were older than 60 years were excluded from the cohort study as they might have aging-related health issues (e.g., multiple chronic diseases and treatments, changes in physical and cognitive abilities, increased vulnerability to stressors) which could confound the outcome measures (High et al., 2012).

3.3 Recruitment and data collection

Before the field data collection, all research associates from the local CDC and hospitals/clinics received a three-day training course which covered topics on research ethics, assessment methodology and survey skills, including how to minimize the social desirability bias. A one-day booster training session was also conducted prior to each of the follow-up assessments. The booster session briefly rehearsed the survey skills and reviews research ethics. Based on the systematic sampling, once an eligible PLWH was randomly selected, the local team members contacted patients to confirm eligibility, discussed about the benefits and risks of the study, and invited them to participate. After obtaining their written informed content, the face-to-face interviews were conducted in private rooms of the clinics. An interviewer-administered questionnaire was used for data collection. Baseline assessment was conduct from November 2017 to February 2018. The recruited participants would be followed up at 6-, 12-, 18-, 24-, 30-, and 36- months. Currently, the 30- month follow-up had been finished. The attrition rate was less than 5% of the participants for each follow-up. Longitudinal data at baseline, 6-, 12-, and 18-month follow-ups were used in the dissertation. Each participant received a gift (e.g., household items) equivalent to US$5.00 (1 USD ≈ 6.5 Chinese Yuan at the time of the survey) at the completion of each assessment. The study protocol was approved by the Institutional Review Boards at both University of South Carolina in the United States and Guangxi CDC in China.

3.4 Key measures

Key measures in this dissertation included CD4 count, viral suppression, HRQoL, HIV-related stigma (i.e., internalized, anticipated, enacted stigma), ART self-efficacy, HIV symptom management self-efficacy, ART adherence, sociodemographic characteristics, depression, and anxiety.

Primary outcomes

CD4 count

CD4 count of each participant at baseline, 6-, 12-, and 18- month follow-ups were retrieved from the electronic health records. According to the guidelines for ART in adults and adolescents with HIV (U.S. Department of Health and Human Services & Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017), the cut-off of 500 cells/µl has clinical implication in evaluating the normal immunologic functioning. Therefore, instead of using the original continuous measure of CD4 count, CD4 count was categorized as a binary variable (< 500 and ≥ 500 cells/µl).

Viral suppression

Plasma viral load of each participant was collected from the electronic health records at each timeframe and used to define viral suppression. As viral suppression could indicate the treatment efficacy, it was used as one of the primary outcomes rather than the original continuous value of viral load. Viral suppression was defined as HIV RNA less than or equal to 50 copies/ml in PLWH's plasma (CDC & National Center for HIV/AIDS, Viral Hepatitis, and TB Prevention, 2018).

Health-related quality of life (HRQoL)

Participants' HRQoL were assessed using the 35- item Medical Outcomes Study HIV Health Survey (MOS-HIV) (Wu et al., 1997). This scale measured 11 dimensions of health including general health perception (5 items), physical functioning (6 items), role functioning (2 items), social functioning (1 item), cognitive functioning (4 items), pain (2 items), mental health (5 items), energy/fatigue (4 items), health distress (4 items), quality of life (1 item), and health transition (1 item). The sum score of each dimension was calculated and transformed to the final score ranging from 0 to 100 according to formula 1 (Delate & Coons, 2001; Hays & Shapiro, 1992; Ware & Sherbourne, 1992; Wu et al., 1997). The total score of HRQoL was calculated using the sum scores from 11 dimensions and transformed to the score ranging from 0 to 100 based on the same formula. The Cronbach's alpha of MOS-HIV scale was 0.93 at baseline.

$$\text{Final score} = \frac{\text{Observed score-possible minimum}}{\text{Possible maximum-possible minimum}} * 100 \qquad \text{Formula (1)}$$

Independent variables

Sociodemographic characteristics

In this dissertation, sociodemographic characteristics included age (year), time since HIV diagnosis (year), duration of ART (year), gender (0 = female, 1 = male), marital status (1 = single/separated, 2 = married/cohabitated, 3 = divorced/widowed), ethnicity (0 = Non-Han, 1 = Han), types of residence (1 = city, 2 = county, 3 = rural), education attainment (0 = less than or equal to middle school, 1 = high school or above), employment (1 = unemployed, 2 = part time, 3 = full time), levels of monthly income (1 = no more than 1,999 Yuan, 2 = 2,000~3,999 Yuan, 3 = at least 4,000 Yuan), transmission modes (0 = others [transfusion/injection drug use/unknown/others], 1 = sexual activity), weight, and height. Body mass index (BMI) was calculated using weight and height and categorized as underweight (less than 18.5), normal/healthy weight (18.5 ~ 24.9), and overweight/obese (more than 24.9).

Internalized stigma

Internalized stigma was measured using an 8-item scale derived from the Berger HIV Stigma Scale (Berger et al., 2001). These eight items were used to assess the "negative self-image" among PLWH in the original scale. Participants were asked to rate their agreement to the statement, including "I feel I'm not as good as others because I have HIV", "I feel guilty because I have HIV", and "Having HIV makes me feel unclean". The response options were rated from "strongly disagree (1)" to "strongly agree (4)". The response options were rated from "strongly disagree (1)" to "strongly agree (4)". The total score of these eight items was used as the indicator of internalized stigma, with a higher score indicating a higher level of internalized stigma. This scale had good reliability at baseline (Cronbach's alpha = 0.94).

Anticipated stigma

Anticipated stigma was assessed using a 9-item scale derived from the Health Stigma Framework (Earnshaw et al., 2013). This scale assessed the expectation of HIV-related stigma from family members, community, and healthcare providers. The item samples were "Family members will avoid touching me", "Community managers will refuse to provide me with social services", and "Healthcare providers will treat me with less respect". The response options were "definitely not (1)", "probably not (2)", "not sure (3)", "probably (4)", and "definitely (5)". The sum score was used as a composite score ranging from 9 to 45, with higher score indicating higher levels of anticipated stigma. The Cronbach's alpha of this scale at baseline assessment was 0.92.

Enacted stigma

Enacted stigma was evaluated using the 16-item checklist adapted from a previous study (Yi et al., 2015). PLWH were asked whether they had some actual experiences of being stigmatized due to HIV in the past six months, including "Being excluded from social gathering or activities", "Being excluded from family activities", and "Being physically assaulted". Participants who answered "yes (1)" were considered to have the experience of being stigmatized while those who answered "no (0)" were considered to have no such experience. The total score of the 16 items was used as a composite score, with a higher score indicating more experiences of being stigmatized in the last six months. The enacted stigma scale also showed good reliability at baseline (Cronbach's alpha=0.89). In Study 1, enacted stigma was used as a continuous variable.

It was categorized as a binary variable using zero as a cutoff and to define stigmatized experiences (0 = No, 1 = Yes) in Study 2.

ART self-efficacy

ART self-efficacy was assessed using a 10-item scale adapted from the Self-efficacy for Appropriate Medication Use Scale (SEAMS) (Risser, Jacobson, & Kripalani, 2007; Zhang et al., 2016). PLWH were asked "How confident are you that you can take your medicines correctly under the following scenarios"? Sample items were "When you take several different medicines each day" and "When you are away from home". Item response options were ranging from "not confident (1)" to "confident (3)". The sum score of these ten items was used as a composite score ranging from 10 to 30, with a higher score indicating a higher level of ART self-efficacy. The Cronbach's alpha of this scale at baseline assessment was 0.95.

HIV symptom management self-efficacy

HIV symptom management self-efficacy was constructed by six items from the Self-efficacy for Managing Chronic Disease Scale (Eller et al., 2014) and four items about participants' confidence in symptom management (Lorig, Sobel, Ritter, Laurent, & Hobbs, 2001). The four items evaluate participants' confidence in keeping symptoms from interfering with social functions, deciding when to see a doctor, forming a plan for symptom management, and controlling medication-induced side effects (Lorig et al., 2001). The overall scale evaluated PLWH's efficacy in controlling HIV-related symptoms. One sample item was "I am confident that I can manage HIV medication side effects." Item options ranged from "totally disagree (1)" to "totally agree (5)". A composited score of HIV symptom management self-efficacy was calculated by summing these 10 items, with higher score indicating more confidence in HIV symptom management. The HIV symptom management self-efficacy scale had good reliability at baseline (Cronbach's alpha = 0.96).

ART adherence

To minimize the self-report bias related to self-report measures of ART adherence, a multiple-item approach was employed to assess adherence to ART in original cohort study (Chesney et al., 2000; Da, Li, Qiao, Zhou, & Shen, 2018; Simoni et al., 2006). Five measures derived from the Adult AIDS Clinical Trials Group (AACTG) adherence instrument and adapted to the cohort study were used to inquiry participants about their levels of ART adherence (Chesney et al., 2000). The measure of ART adherence had been validated in different countries and culture contexts (Chesney et al., 2000; Da et al., 2018; Reynolds et al., 2007) and could be used as a robust instrument for evaluating adherence behaviors among HIV population.

An overall score was calculated according to the following procedure (Da et al., 2018) (Table 3.1). First, participants reported the days of completing their prescribed ART doses within four specified timeframes (last three days, last weekend, last two weeks, last month [30 days]). For the last three-day and weekend adherence measures, participants were asked to report the number of doses taken and the number of expected doses during these two timeframes. Percentage adherence was calculated dividing doses taken by doses expected. For the one-month and two-week days taken measures, participants were asked to report the number of days they took all doses of their HIV medication as prescribed. Percentage adherence was calculated by dividing the reported number of days by 30 days (or 14 days). These responses were then converted into a percentage of prescribed doses and recoded into 0 (< 90%) or 1 (≥ 90% of prescribed doses) according to the Chinese guideline for ART treatment. Second, whether participants adhere to their prescribed doses (1 = always, 2 = very often, 3 = sometimes, 4 = rarely, 5 = never) was used as the fifth adherence measure. Participants who always adhered to their prescription were coded as “Yes (1)” while others were coded as “No (0)”. Finally, by summing scores of the above five measures, a composite score was calculated. The sum score ranges from 0 to 5. PLWH who scored 5 were considered as optimal adherence to ART while those who scored less than 5 were considered as suboptimal adherence to ART. The Cronbach’s alpha of this measure at baseline assessment was 0.72. In both Studies 1 and 2, the binary measure of ART adherence was used for the longitudinal data analysis.

Table 3.1 Items and calculation of ART adherence

Items	Questions	Scoring
1	Please report the number of doses taken and the number of expected doses in your prescribed ART during the last three days.	$\% = \frac{\text{Number of doses taken}}{\text{Number of expected doses}} * 100\%$
2	Please report the number of doses taken and the number of expected doses in your prescribed ART during the last weekend.	If percentage adherence (%) is equal to or larger than 90%, items 1 or 2 will be coded as 1. Otherwise, these two items will be coded as 0.
3	Please report the number of days you took all doses of your prescribed HIV medication during the last two weeks.	$\% = \frac{\text{Number of days with all dose}}{\text{30 days or 14 days}} * 100\%$
4	Please report the number of days you took all doses of your prescribed HIV medication during the last month.	If percentage adherence (%) is equal to or larger than 90%, items 3 or 4 will be coded as 1. Otherwise, these two items will be coded as 0.
5	Did you always adhere to your prescription? 1. Always; 2. Very often; 3. Sometimes; 4. Rarely; 5. Never.	If the response to this item is "Always", item 5 will be coded as 1. Otherwise, this item will be coded as 0.
Sum score	Sum sore = Item 1 + Item 2 + Item 3 + Item 4+ Item 5 The sum sore is ranging from 0 to 5. PLWH who score 5 will be considered as having optimal adherence to ART while those who score less than 5 will be considered as having suboptimal adherence to ART.	

Depression

PLWH were assessed their levels of depression using the 10-item Center for Epidemiologic Studies Depression (CES-D) Scale. The CES-D scale had been widely used, and its validity and reliability had been established in Chinese population (Yu, Lin, & Hsu, 2013). It captured depressed affect (3 items), somatic symptoms (5 items), and positive affect (2 items). The response options ranged from “rarely or none of the time (0)” to “all of the time (3)”. The summed score ranging from 0 to 30 was used to reflect the levels of depression, with a higher score indicating a higher level of depression. The CES-D scale had good reliability at baseline assessment (Cronbach’s alpha= 0.85).

Anxiety

Anxiety was measured using the Brief Anxiety Scale (Zung, 1971), which had been validated in Chinese population (Zhang, Liu, Li, Mao, & Yuan, 2015). PLWH were asked their feelings (e.g., “I feel easily upset or panicked”, “I experience headache and a sore neck”) about anxiety disorders in the past week. The original scale included 20 items which were scored from “never or seldom (1)” to “often (4)”. The total score ranged from 20 to 80. However, due to issue of translation, two items (“My hands are usually dry and warm”, “I fall asleep easily and get a good night’s rest”) could not capture their original meanings, which resulted in the Cronbach’s alpha of original scale equal to 0.80. After deleting these two items, the Cronbach’s alpha was significantly improved to 0.88. Hence, the rest of the items were used to calculate the final anxiety score ranging from 18 to 72, with a higher score indicating a higher level of anxiety.

3.5 Data analysis

3.5a Data analysis in Study 1

First, descriptive statistics were reported on all the variables used in the dissertation. *Mean* and *standard deviation* (*SD*) were used to describe the continuous variables while *frequencies* and *percentages* were used for categorical variables. Second, changes of clinical outcomes and independent variables across the time were tested. Analysis of variance (ANOVA) was used to test the changes of continuous variables while Chi-square test was used for categorical variables.

Third, hierarchical longitudinal analysis was conducted to carry out aim 1. Hierarchical regression is a way to show if variables of interest could explain a statistically significant amount of variance in outcome after accounting for all other variables (Kim, 2016). During the hierarchical longitudinal analysis, the first model included sociodemographic characteristics and other confounders. In the next step (model 2), important variables were added to model 1.

Before the multivariable analysis, bivariate analysis was conducted to examine the relationship between each clinical outcome and independent variable using generalized linear mixed model. Crude odds ratio (*OR*) or regression coefficient and the 95% confidence interval (*CI*) were reported in bivariate analysis for each clinical outcome. Variables with *p*-values less than 0.10 were controlled as covariates in multivariable analysis. In hierarchical longitudinal analysis, for CD4 count and viral suppression, generalized linear mixed model with categorical outcome was employed to examine the hypotheses. First of all, covariates and duration of ART was controlled as confounders in model 1 after adjusting for the repeated measurements. Then, psycho-behavioral factors, such as ART self-efficacy, HIV symptom management self-efficacy, depression, anxiety, and ART adherence, were added to model 1 and examined their impacts on the outcomes (model 2). Finally, to examine the impacts of internalized, anticipated, and enacted stigma on outcomes, these three types of stigma were added to model 2 and tested in model 3 simultaneously. As CD4 count and viral suppression were binary outcomes, the distribution was specified as "binomial distribution", and link function was defined as "logit link function". To model the correlations of CD4 count and viral suppression at baseline, 6-, 12-, and 18-month follow-ups, correlation structures (e.g., unstructured covariance, autoregressive covariance, exchangeable covariance, and independent covariance) were examined, and multiple indices (i.e., Queensland Investment Corporation [*QIC*] and *QICu*) were used for evaluating the goodness of fit (Cui & Qian, 2007). Model with the smallest values of the *QIC* and *QICu* were considered as having the best model fit (Cui & Qian, 2007). If the best models selected by *QIC* and *QICu* were inconsistent, *QIC* was used as the final criteria for model selection (Cui & Qian, 2007). Adjusted *OR* (*AOR*) and its 95% *CI* were reported.

In terms of HRQoL, hierarchical generalized linear mixed model with continuous outcome was used to carry out aim 1. A similar modelling procedure was conducted to examine the impacts of sociodemographic characteristics, psycho-behavioral factors, and HIV-related stigma on HRQoL after adjusting for the repeated measures. Besides the covariates and potential confounders, CD4 count was adjusted during the analysis. Correlation structures (e.g., unstructured covariance, autoregressive covariance, and heterogeneous autoregressive covariance) were examined, and Log likelihood value, Akaike Information Criterion [*AIC*], Corrected AIC [*AICC*], and Bayes Information

Criterion [*BIC*] were used as the indicators for model selection (Fitzmaurice, Laird, & Ware, 2011). Model with smaller *AIC*, *AICC*, *BIC* had better model fit (Fitzmaurice et al., 2011). Regression coefficient (β) and its 95% *CI* were reported in this dissertation. Pseudo R square (R^2) was reported to evaluate percentage of variance being accounted for in each model (Edwards, Muller, Wolfinger, Qaqish, & Schabenberger, 2008) during the process of hierarchical longitudinal analysis. All the analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

3.5b Data analysis in Study 2

Latent growth curve model (LGCM) was the major model used in Study 2. It allows for the estimation of inter-individual variability in intra-individual change patterns through two latent factors—the intercept (the initial value of variable of interest) and slope (the change rate of variable of interest) (Curran, Obeidat, & Losardo, 2010; Duncan & Duncan, 2004). It could be applied to investigate the trajectories for both continuous and categorical variables (Wang & Wang, 2019). The change patterns (i.e., linear, quadratic, and cubic changes) of variables of interest could be defined by designing their time scores (Wang & Wang, 2019). Using LGCM to perform mediation analysis among the slopes (change) of key variables has strong ability for causal inference (Cheong et al., 2003).

First, measurement models of all key variables in conceptual model were constructed using their original values and unconditional LGCM (Wang & Wang, 2019). As Study 2 focused on examining the longitudinal mediating effects of psycho-behavioral mediators, the changes of all variables of interest were defined as linear trend (time scores: 0, 1, 2, 3). In this process, LGCM with continuous outcomes were used for internalized stigma, anticipated stigma, ART self-efficacy, HIV symptom management self-efficacy, and HRQoL while LGCM with binary outcomes were used for enacted stigma, ART adherence, CD4 count, and viral suppression. In the process of LGCM with binary outcomes, logit link function was specified. Multiple indices, such as χ^2, χ^2/degree of freedom (*df*), *p*-value, *Comparative Fit Index* (*CFI*), *Root Mean Square Error of Approximation* (*RMSEA*), and *Standardized Root Mean Residual* (*SRMR*), were used to evaluate the model fit of each measurement model. For continuous variables, smaller χ^2 value, $\chi^2/df \leq 3.00$, $p > 0.05$, $CFI > 0.95$, $RMSEA \leq 0.06$, and $SRMR \leq 0.08$ indicated better model fit (Muthen & Muthen, 2018). In terms of binary variables, smaller χ^2 value, $\chi^2/df \leq 3.00$, and $p > 0.05$ indicated better model fit (Muthen & Muthen, 2018; Schermelleh-Engel, Moosbrugger, & Müller, 2003). *Mean* and *standard error* (*SE*) were used to describe intercept and slope while *r* was used to describe the correlation between them. Since all continuous variables were not in normal distribution, using their original values to construct measurement models could not obtain good model fits and capture the information of all participants sufficiently. Therefore, standardized transformation was employed to re-estimate the intercepts and slopes of all continuous variables before mediation analysis.

Second, the estimated intercepts and slopes of all key variables in conceptual model were outputted for bivariate analysis and longitudinal mediation analysis. Spearman correlation analysis was used to examine the correlations among intercepts or slopes of all key variables in conceptual model. Bivariate analysis of the slopes of clinical outcomes (i.e., CD4 count, viral suppression, and HRQoL) and sociodemographic characteristics, depression, and anxiety were conducted. Spearman correlation analysis was used for examining the correlations between continuous variables while Wilcoxon two-sample test or Kruskal-Wallis test were used for the relationships between slopes and categorical variables.

Third, intercepts and slopes of all key variables were used for mediation analysis after adjusting for covariates with *p*-values less than 0.05 in bivariate analyses. First of all, intercept and slope were specified as correlating with each other for each key variable, and path model was constructed based on the conceptual framework. Then, based on the model trimming strategies (Ullman, 2001), paths with *p*-values larger than 0.05 were deleted. Furthermore, path model was modified to improve its model fit based on the modification indices and theoretical knowledge (Ullman, 2001; Wang & Wang, 2019). Path coefficient and its 95%*CI*, standardized coefficient, and *p*-value were reported. Finally, longitudinal mediating effects from the slopes of HIV-related stigma to those of clinical outcomes through the slopes of psycho-behavioral mediators were tested using bias-corrected bootstrap procedure based 1,000 bootstrap samples (Wang & Wang, 2019). Bias-corrected 95%*CI* of the indirect pathways were reported (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Delta *z* score was used as a statistics to evaluate indirect effects (Muthen & Muthen, 2018). Robust maximum likelihood estimation (estimator=MLR) was used to estimate the parameters, and full information maximum likelihood (FIML) estimation approach was used to handle missing data. Multiple indices were used to evaluate the model fit. Same indices, such as χ^2, χ^2/df, *p*-values, *CFI*, *RMSEA*, and *SRMR*, were used to assess the model fit. Bivariate analysis was performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). LGCM and mediation analysis were performed using Mplus version 7.0 (Muthen & Muthen, Los Angeles, CA).

3.6 Overall analytic considerations for the dissertation

Prior to data analysis specific to each aim, overall analytic considerations associated with appropriate analysis were carefully assessed and considered in data management and cleaning. The two studies in this dissertation pursued preliminary analyses including identification and adjustment of covariates, collinearity, missing data, and outliers. During the longitudinal data analysis, change patterns (e.g., linear and non-linear patterns) were evaluated and considered.

3.6a Covariates

Covariates adjusted in both Studies 1 and 2 were selected based on the bivariate analysis and empirical evidences. Bivariate analysis was used to test the relationships between sociodemographic characteristics and clinical outcomes. Sociodemographic characteristics with specific *p*-values ($p \leq 0.10$ in Study 1; $p \leq 0.05$ in Study 2) were considered as potential covariates. Potential covariates supported by empirical evidences and associated with clinical outcomes were adjusted in the final model. As psychosocial distress, such as depression and anxiety, were closely associated with clinical outcomes (Andrinopoulos et al., 2011; Jain et al., 2020; Khare, Rajpoot, & Dubey, 2020; Shi et al., 2020; Yang, Thai, & Choi, 2016), they were also adjusted as covariates in both Studies 1 and 2.

Sociodemographic characteristics and psychosocial distress were determined as time-varying or time-invariant based on the study design. For instance, only age, time since HIV diagnosis, duration of ART, employment, BMI, depression, and anxiety were collected at all four-wave datasets. Therefore, these variables were considered as time-varying covariates during the longitudinal analysis in Study 1. All potential covariates at baseline assessment were controlled in the mediation analysis of Study 2.

3.6b Collinearity

Collinearity might exist during the longitudinal data analysis and influence the parameter estimation. The collinearity among variables of interest were tested using "PROC REG" process in SAS. Condition index, variance of inflation (VIF), and value of tolerance were used to evaluate whether there was collinearity among them (Wicklin, 2020). The criteria of collinearity were: (1) condition index was larger than 30; (2) VIF was larger than 10; and/or (3) value of tolerance was less than 0.2 or 0.1 (Wicklin, 2020). In this dissertation, collinearity was identified between time since HIV diagnosis and ART. As these two variables had similar conceptual meaning and strong correlation, one of them was controlled in the final model based on their correlation with each clinical outcome. As duration of ART had direct impacts on viral suppression and CD4 count, it was controlled as a covariate if viral suppression and CD4 count were the major outcomes in the analysis. In terms of the HRQoL, as it is closely associated with time since HIV diagnosis, time since HIV diagnosis was controlled as one of the covariates in the analysis (Patel et al., 2009).

3.6c Missing data

Missing data is a common but important issue in longitudinal data analysis. The preliminary assessment of the four-wave datasets used in this dissertation found that the attrition rate was less than 5% of the participants for each follow-up. As the proportions of missing value were less than 10%, listwise deletion was used as a default method for handling missing data in longitudinal data analysis (Dong & Peng, 2013; Schafer, 1999). For the generalized linear mixed model in Study 1, it deleted the observations for which an outcome had missing data (Fitzmaurice et al., 2011).

In terms of the LGCM in Study 2, missing data was handled using FIML estimation approach for continuous variables while listwise deletion was used for categorical variables. FIML approach estimates the parameters using the complete observations (Graham, 2009). Based on the assumption of missing completely at random (MCAR) or missing at random (MAR), FIML could effectively handle missing data in latent variable analysis (Graham, 2009). As the percentage of missing data at each follow-up was low, MAR was assumed. FIML was used to estimate the parameters of LGCM with continuous variables. In mediation analysis, FIML was also used to handle the missing values as slope was a continuous variable.

3.6d Outliers

Multivariable linear regression was conducted to examine the outliers among all continuous variables using SAS "PROC REG" process. Scatter plot, residual plot, Cook's distance, Leverage statistics, and Studentized residual were used to detect the outliers among variables of interest. Observations with Cook's distance close to or larger than 1, Leverage statistics larger than $2*(p+1)/n$ (p is the number of parameters in regression model and n is the sample size), and/or the absolute value of Studentized residual larger than 2 were considered as outliers (Chartier & Cousineau, 2010). Once the outliers or influential cases were identified, these observations were double-checked in the original dataset to see whether there were any mistakes on data cleaning, coding, and management. For the outliers or influential cases without any mistakes in data collection and management, they were kept for further analyses. However, for the illegitimate outliers, they were recoded as missing values.

3.6e Change pattern

Change pattern is also an important issue to consider in longitudinal data analysis. However, as most variables of interest only had small changes across the time and this dissertation aims to test the impacts of independent variables on clinical outcomes, in both Studies 1 and 2, the changes of key variables were defined as linear trends. Using linear trend to define the change patterns of key variables in LGCM could reduce the risk of model misidentification.

CHAPTER 4

LONGITUDINAL IMPACTS OF INTERNALIZED, ANTICIPATED, AND ENACTED STIGMA ON CLINICAL OUTCOMES AMONG PLWH: A PROSPECTIVE COHORT STUDY

4.1 Abstract

As we are approaching the accomplishment of "90-90-90" goal, improving the clinical outcomes among people living with HIV (PLWH) becomes a critical component of HIV treatment and care continuum. Previous studies confirmed the impacts of overall measure of HIV-related stigma on clinical outcomes. However, few studies have distinguished the separate effects of different types of HIV-related stigma on clinical outcomes after accounting for psycho-behavioral factors. This study aimed to investigate the relationships between internalized, anticipated, enacted stigma and clinical outcomes using hierarchical longitudinal approach.

A prospective cohort study was conducted in Guangxi, China among 1,198 PLWH. Data at baseline, 6-, 12-, and 18- follow-ups were used for analysis. CD4 count, viral suppression, and health-related quality of life (HRQoL) were the major clinical outcomes in this study. Internalized, anticipated, and enacted stigma were measured using separate scales. Hierarchical generalized linear mixed model was used to examine the impacts of internalized, anticipated, and enacted stigma on clinical outcomes after

adjusting for psycho-behavioral factors (i.e., antiretroviral therapy [ART] self-efficacy, HIV symptom management self-efficacy, ART adherence, depression, and anxiety) and covariates.

Among the 1,198 PLWH, the viral suppression improved while HRQoL decreased significantly. CD4 count had slight improvement over time but this change was not significant. All three types of HIV-related stigma changed significantly. Hierarchical analysis revealed that the three HIV-related stigma explained additional variances in clinical outcomes after adjusting for psycho-behavioral factors and covariates. Internalized (β=-0.78, 95% confidence interval [*CI*]: -1.07~-0.49), anticipated (β=-0.84, 95% *CI*: -1.12~-0.55), and enacted stigma (β=-0.83, 95% *CI*: -1.10~-0.56) could significantly reduce HRQoL but not CD4 count and viral suppression. Psycho-behavioral factors showed differential effects on the three clinical outcomes.

HIV-related stigma could explain additional information of clinical outcomes and showed differential impacts. Future studies are needed to investigate the psycho-behavioral mechanisms of HIV-related stigma on clinical outcomes. To improve clinical outcomes among PLWH effectively, interventions are warrant to not only target HIV-related stigma but also to promote resilience which could alleviate the negative impacts of HIV-related stigma.

4.2 Introduction

Global HIV epidemic and progress in "90-90-90" goals

The widespread application of antiretroviral therapy (ART) has dramatically reduced the mortality of HIV infection and deterred further transmission (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2020a, 2020b). However, currently the

HIV epidemic is still a critical public health challenge globally including in China (UNAIDS, 2020b). The number of people living with HIV (PLWH) in China has steadily increased since 2005, and there were more than 1.25 million cumulative diagnosed and undiagnosed cases by the end of 2018, with an estimated of 80,000 new cases diagnosed during the same year (Wu, Chen, Scott, & McGoogan, 2019; Wu, McGoogan, & Detels, 2021).

To control the global HIV epidemic and AIDS-related deaths, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the “90-90-90” goals in 2014 (Marsh et al., 2019). These goals included at least 90% of the diagnosis, 90% of the treatment, and 90% of the viral suppression among PLWH by the end of 2020 (Marsh et al., 2019). Since 2016, research also suggested that health-related quality of life (HRQoL) should be the fourth goal for HIV treatment and care continuum. PLWH with considerable levels of CD4 cells and viral suppression still need to contend with other challenges, such as potential side effects of ART, the possibility of treatment failure, and other comorbidities (Andersson et al., 2020; Lazarus et al., 2016; Webster, 2019). HRQoL is a comprehensive construct of health quality as it could reflect the disease burden across four main dimensions (i.e., physical health, psychological health, social functioning, and perception about general health) (Ashing-Giwa, 2005; Ruiz Perez et al., 2005; Wu, Hays, Kelly, Malitz, & Bozzette, 1997). The announcement from UNAIDS emphasized the importance of clinical outcomes (i.e., CD4 count, viral suppression, and HRQoL) among PLWH on ART.

The progress of clinical outcomes among PLWH still does not meet the “90-90-90” goals. Among the 38 million PLWH worldwide, only 62% of them were on ART and

53% had achieved viral suppression in 2018 (Marsh et al., 2019). In China, by the end of 2018, 94.2% of the PLWH had suppressed viral load (Ma et al., 2018; Wu, 2016) but spatial variation in viral suppression was found. PLWH from rural provinces (e.g., Yunnan, Guangxi) were less likely to achieve viral suppression than those from urban provinces (e.g., Guangdong) (Chen et al., 2014; Huang et al., 2015). In terms of CD4 count, an important indicator of immunologic functioning, a nationwide retrospective cohort study in China found that nearly 80% of the PLWH on ART had their CD4 count between 200 ~ 349 cells/μl (Hu et al., 2017), which were still not within the typical range for a healthy immune system (CD4 count ≥ 500 cells/μl). Due to HIV, PLWH also experience lower levels of HRQoL than the general population (Lan et al., 2015).

Clinical outcomes and HIV-related stigma

Prior research summarized some psycho-behavioral factors related to clinical outcomes among PLWH. These factors included but are not limited to HIV-related stigma (Bhat et al., 2015; Darlington & Hutson, 2017), treatment-related self-efficacy (Zeng et al., 2020; Zhou, Li, Qiao, Shen, & Zhou, 2020), ART adherence (Adiga, Adiga, & Bn, 2016; Arnsten et al., 2001; Reis, Lencastrez, Jonsson, & Guerra, 2020; Wood et al., 2004), and psychological distress (Ajose, Mookerjee, Mills, Boulle, & Ford, 2012; Gore-Felton & Koopman, 2008; Pence, 2009). Among these factors, HIV-related stigma, as a chronic stressor among PLWH, is a well-established factor closely related to clinical outcomes.

HIV-related stigma is defined as a “discrediting and tainting social label” because of HIV. According to the Health Stigma Framework, HIV-related stigma included internalized, anticipated, and enacted stigma (Earnshaw & Chaudoir, 2009; Earnshaw, Smith, Chaudoir, Amico, & Copenhaver, 2013), which reflect the cognitions, beliefs, and experiences of discrimination against PLWH, respectively. Internalized stigma refers to the cognitive process of believing that the negative attributes related to HIV are true of the self (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013). PLWH with high levels of internalized stigma would apply these negative beliefs to themselves and believe that they are devalued or bad as compared to others (Quinn & Earnshaw, 2011; Sayles, Wong, Kinsler, Martins, & Cunningham, 2009). Anticipated stigma makes PLWH believe that they may receive negative treatment if others know their HIV status (Quinn & Earnshaw, 2011). It is closely related to the fears of being discriminated among PLWH. Enacted stigma is the actual experience of being discriminated by others (Quinn & Earnshaw, 2011). When HIV status is known either through voluntary disclosure or unintended disclosure, PLWH would be treated in stigmatizing ways. These three types of HIV-related stigma could inhibit health-seeking behaviors, timely diagnosis, prevent PLWH from treatment and care, and impair their health outcomes (Alonzo & Reynolds, 1995; Andersson et al., 2020; Goffman, 1963). However, currently, limited research investigated the direct impacts of internalized, anticipated, and enacted stigma on clinical outcomes simultaneously. Instead, most extant research only focused on the overall HIV-related stigma or one or more types (Fuster-Ruizdeapodaca, Molero, Holgado, & Mayordomo, 2014; Logie et al., 2019; Parcesepe et al., 2020). These studies might ignore the nuanced differences among them and could not adequately inform tailored intervention to each type of stigma and clinical outcomes.

HIV-related stigma in China

PLWH in China suffer from serious HIV-related stigma. The Chinese culture, such as collectivism and family responsibilities, may cultivate HIV-related stigma against PLWH (Liu et al., 2006). The collectivist culture subordinates individual interests to those of the group and requires people in the same group to maintain dignity, respect, and social status in the social structure (Hui & Triandis, 1986; Kleinman et al., 1995; Murray-Johnson et al., 2001; Triandis, Bontempo, & Villareal, 1988). People would be devalued or condemned if they do not comply with the rules in collectivist culture. As HIV infection is closely related to stigmatizing behaviors, such as commercial sex, casual sex, and injection drug use, PLWH would be devalued by the collectivist society as the collective value is considered to be destroyed by them (Liu et al., 2006). What is more, the Chinese culture emphasizes family responsibilities, such as maintaining and protecting family (males' responsibilities) and taking care of the home, the children, and the rest of the family (females' responsibilities). Due to HIV, many PLWH suffer from serious health burden and could not fully take the family responsibilities. Particularly, some PLWH who are sexual minorities could not have children to maintain the family bloodline, which would put them at risk of stigma (Li, Holroyd, Lau, & Li, 2015). However, few studies investigated the negative impacts of HIV-related stigma on clinical outcomes among PLWH in China.

PLWH in Guangxi are vulnerable to HIV-related stigma. Guangxi is a resource-limited province located in southern China. Therefore, compared with other developed provinces with relatively sufficient resources, Guangxi is more conservative in regard to Chinese culture. Additionally, the HIV epidemic in Guangxi is a rural phenomenon with large number of PLWH living in rural areas, in low socioeconomic status, and being infected mostly through sexual activity (Wang, 2013; Yang et al., 2019). For instance, an existing study found that from 1996 to 2017, the primary routes of HIV transmission changed from infection drug use to sexual contacts including heterosexual and male-to-male sexual activity (Chen et al., 2019). Hence, due to the conservative culture, limited knowledge of HIV infection, and local HIV epidemic, PLWH in Guangxi may experience high levels of HIV-related stigma. Therefore, investigations are needed to explore the separate impacts of internalized, anticipated, and enacted stigma on clinical outcomes among this vulnerable population, which could provide empirical evidences for stigma intervention design among PLWH and improving their health outcomes.

Research goals and hypotheses

To address these knowledge gaps, the current study leveraged data derived from a prospective cohort and hierarchical regression approach and aimed to investigate the effects of internalized, anticipated, and enacted stigma on the three clinical outcomes (i.e., CD4, viral suppression, and HRQoL) among PLWH in Guangxi, China. We assumed that all three types of stigma had significant and negative impacts on clinical outcomes.

4.3 Methods

Study design and setting

Data used in this study were derived from a prospective cohort study among PLWH in Guangxi, China. From 2014 to 2018, Guangxi was consistently ranked third across the 31 provinces in China in terms of the total number of HIV cases (Wu et al., 2019). By 2018, there were over 86,000 PLWH reported in Guangxi (Guangxi Center for

Disease Control and Prevention [CDC], 2018). With the assistance and collaboration of Guangxi Center for Disease Control and Prevention (CDC), six major public hospitals/clinics in five cities with the largest number of PLWH under care were selected as study sites. The number of PLWH in each study site ranged from 1,386 to 7,389 at the time of baseline assessment.

Participants

Using a systematic sampling approach, PLWH who fulfilled the eligibility were invited to participate in the cohort study. The inclusion criteria for the cohort study were PLWH who: 1) aged between 18 and 60 years old; 2) had a confirmed diagnosis of HIV; and 3) had no plan to relocate outside of Guangxi in the next 12 months. PLWH who had mental and/or physical inability to answer assessment questions and/or who were currently incarcerated or institutionalized were excluded from the study. Additionally, PLWH who were older than 60 years were excluded from the study due to aging-related health issues (e.g., multiple chronic diseases and treatments, changes in physical and cognitive abilities, increased vulnerability to stressors) which could confound the outcome measures (High et al., 2012).

Recruitment and data collection

Before the data collection, all research associates from the local CDC and hospitals/clinics received a three-day training course which covered topics on assessment methodology and survey skills. A one-day booster training session was also conducted prior to each of the follow-ups. The booster session briefly rehearsed the survey skills and reviews research ethics. Based on the systematic sampling, once eligible PLWH were randomly selected, the local team members confirmed the patients for eligibility, scheduled a meeting to discuss about the benefits and risks of the study, and invited them to participate. After obtaining their written informed consent, the face-to-face interviews were conducted in private rooms of the clinics. An interviewer-administered questionnaire was used for data collection. Baseline assessment was conducted from November 2017 to February 2018. The recruited participants were followed up at 6-, 12-, 18-, 24-, 30-, and 36- months. Longitudinal data at baseline, 6-, 12-, and 18-month follow-ups were used in this study. Each participant received a gift (e.g., household items) equivalent to US$5.00 (1 USD ≈ 6.5 Chinese Yuan at the time of the survey) at the completion of the interview. The study protocol was approved by the Institutional Review Boards at both University of South Carolina in the United States and Guangxi CDC in China.

Measures

CD4 count

CD4 count of each participant at baseline, 6-, 12-, and 18- month follow-ups were retrieved from their electronic health records. According to the guidelines for ART in adults and adolescents with HIV (U.S. Department of Health and Human Services & Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017), the cut-off of 500 cells/µl has clinical implication in evaluating the normal immunologic functioning. Therefore, CD4 count was categorized as a binary variable (< 500 and ≥ 500 cells/µl).

Viral suppression

Plasma viral load of each participant was collected from the electronic health records at each timeframe and used to define viral suppression. As viral suppression is an indicator of treatment efficacy, it was used as one of the primary outcomes rather than the original continuous value of viral load. Viral suppression refers to HIV RNA less than or equal to 50 copies/ml in PLWH's plasma (CDC & National Center for HIV/AIDS, Viral Hepatitis, and TB Prevention, 2018).

Health-related quality of life (HRQoL)

Participants' HRQoL were assessed using the 35- item Medical Outcomes Study HIV Health Survey (MOS-HIV) (Wu et al., 1997). This scale measured 11 dimensions of health including general health perception, physical functioning, role functioning, social functioning, cognitive functioning, pain, mental health, energy/fatigue, health distress, quality of life, and health transition. The sum score of each dimension was calculated and transformed to the final score ranging from 0 to 100 as suggested by previous studies (Delate & Coons, 2001; Hays & Shapiro, 1992; Ware & Sherbourne, 1992; Wu et al., 1997). The total score of HRQoL was calculated using the sum scores of the 11-dimension and then transformed to the score ranging from 0 to 100. The MOS-HIV showed good reliability among the participants at baseline (Cronbach's alpha = 0.93).

Sociodemographic characteristics

PLWH reported their sociodemographic characteristics including age (year), time since HIV diagnosis (year), duration of ART (year), gender (0 = female, 1 = male), marital status (1 = single/separated, 2 = married/cohabitated, 3 = divorced/widowed), ethnicity (0 = Non-Han, 1 = Han), types of residence (1 = city, 2 = county, 3 = rural), education attainment (0 = less than or equal to middle school, 1 = high school or above), employment (1 = unemployed, 2 = part time, 3 = full time), levels of monthly income (1 = no more than 1,999 Yuan, 2 = 2,000~3,999 Yuan, 3 = at least 4,000 Yuan), transmission modes (0 = others [transfusion/injection drug use/unknown/others], 1 =

sexual activity), weight, and height. Body mass index (BMI) was calculated using weight and height and categorized as underweight (less than 18.5), normal/healthy weight (18.5 ~ 24.9), and overweight/obese (more than 24.9).

Internalized stigma

Internalized stigma was measured using an 8- item scale derived from the Berger HIV Stigma Scale (Berger, Ferrans, & Lashley, 2001). These eight items were used to assess the "negative self-image" among PLWH in the original scale. Participants were asked to rate their agreement to the statement, including "I feel I'm not as good as others because I have HIV", "I feel guilty because I have HIV", and "Having HIV makes me feel unclean". The response options were rated from "strongly disagree (1)" to "strongly agree (4)". The total score of these eight items was used as the indicator of internalized stigma, with a higher score indicating a higher level of internalized stigma. This scale had good reliability at baseline (Cronbach's alpha = 0.94).

Anticipated stigma

Anticipated stigma was assessed using a 9- item scale derived from the Health Stigma Framework (Earnshaw et al., 2013). This scale assessed the expectation of HIV-related stigma from family members, community, and healthcare providers. Sample items were "Family members will avoid touching me", "Community managers will refuse to provide me with social services", and "Healthcare providers will treat me with less respect". The response options were "definitely not (1)", "probably not (2)", "not sure (3)", "probably (4)", and "definitely (5)". The sum score was used as a composite score ranging from 9 to 45, with higher score indicating higher levels of anticipated stigma. The Cronbach's alpha of this scale at baseline assessment was 0.92.

Enacted stigma

Enacted stigma was evaluated using the 16- item checklist adapted from a previous study (Yi et al., 2015). PLWH were asked whether they had actual experiences of being stigmatized due to HIV in the past six months, including “Being excluded from social gathering or activities”, “Being excluded from family activities”, and “Being physically assaulted”. Participants who answered “yes (1)” were considered to have the experience of being stigmatized while those who answered “no (0)” were considered to have no such experience. The total score of the 16 items was used as a composite score, with a higher score indicating more experiences of being stigmatized in the last six months. The enacted stigma scale also showed good reliability at baseline (Cronbach’s alpha = 0.89).

ART self-efficacy

ART self-efficacy was assessed using a 10- item scale adapted from the Self-efficacy for Appropriate Medication Use Scale (SEAMS) (Risser, Jacobson, & Kripalani, 2007; Zhang et al., 2016). PLWH were asked “How confident are you that you can take your medicines correctly under the following scenarios”? Sample items were “When you take several different medicines each day” and “When you are away from home”. Item response options were from “not confident (1)” to “confident (3)”. The sum score of these ten items was used as a composite score ranging from 10 to 30, with a higher score indicating a higher level of ART self-efficacy. The Cronbach’s alpha of the ART self-efficacy scale at baseline was 0.95.

HIV symptom management self-efficacy

HIV symptom management self-efficacy was measured using six items from the Self-efficacy for Managing Chronic Disease Scale (Eller et al., 2014) and four items about participants' confidence in symptom management (Lorig, Sobel, Ritter, Laurent, & Hobbs, 2001). The four items evaluated participants' confidence in keeping symptoms from interfering with social functions, deciding when to see a doctor, forming a plan for symptom management, and managing medication-induced side effects (Lorig et al., 2001). The overall scale evaluated PLWH's efficacy in controlling their HIV-related symptoms. One sample item was "I am confident that I can manage HIV medication side effects." Item options ranged from "totally disagree (1)" to "totally agree (5)". A composite score of HIV symptom management self-efficacy was calculated by summing these 10 items, with higher score indicating more confidence in HIV symptom management. The HIV symptom management self-efficacy scale had good reliability at baseline (Cronbach's alpha = 0.96).

ART adherence

To minimize the self-report bias of self-report measures of ART adherence, a multiple-item approach was employed to assess adherence behavior in the cohort study (Chesney et al., 2000; Da, Li, Qiao, Zhou, & Shen, 2018; Simoni et al., 2006). Five items derived from the Adult AIDS Clinical Trials Group (AACTG) adherence instrument were adapted to ask participants about their levels of ART adherence (Chesney et al., 2000; Da et al., 2018; Reynolds et al., 2007).

An overall adherence score was calculated according to the following procedure (Da et al., 2018). First, participants reported the days of completing their prescribed ART doses within four specified timeframes (last three days, last weekend, last two weeks, last month [30 days]). For the last three-day and weekend measures, participants were asked to report the number of doses taken and the number of expected doses during these two timeframes. Percentage adherence was calculated by dividing doses taken by doses expected. For the one-month and two-week days taken measures, participants were asked to report the number of days they took all doses of their HIV medication as prescribed. Percentage adherence was calculated dividing the reported number of days by 30 days (or 14 days). These responses were then converted into a percentage of prescribed doses and recoded into 0 (< 90%) or 1 (≥ 90% of prescribed doses) according to the Chinese guideline for ART treatment. Second, whether participants adhered to their prescribed doses (1 = always, 2 = very often, 3 = sometimes, 4 = rarely, 5 = never) was used as the fifth adherence item. Participants who always adhered to their prescription were coded as "yes (1)" while others were coded as "no (0)". Finally, by summing scores of the above five items, a composite score was calculated. The sum score ranges from 0 to 5. PLWH who scored 5 were considered as optimal adherence to ART. The five adherence measures showed acceptable reliability at baseline assessment (Cronbach's alpha = 0.72).

Psychological distress

Psychological distress in this study included depression and anxiety. Depression was assessed using the 10- item Center for Epidemiologic Studies-Depression (CES-D 10) Scale. The CES-D scale had been widely used, and its validity and reliability had been established in Chinese population (Yu, Lin, & Hsu, 2013). The response options ranged from "rarely or none of the time (0)" to "all of the time (3)". The summed score ranging from 0 to 30 was used to reflect the levels of depression, with a higher score indicating a higher level of depression. The CES-D scale had good reliability at baseline assessment (Cronbach's alpha= 0.85).

Anxiety was measured using the Brief Anxiety Scale (Zung, 1971), which had been validated in Chinese population (Zhang, Liu, Li, Mao, & Yuan, 2015). PLWH were asked their feelings (e.g., "I feel easily upset or panicked", "I experience headache and a sore neck") about anxiety disorders in the past week. The original scale included 20 items which were scored from "never or seldom (1)" to "often (4)". The total score ranged from 20 to 80. However, due to issue of translation, two items ("My hands are usually dry and warm", "I fall asleep easily and get a good night's rest") could not capture the original meanings, which result in a Cronbach's alpha of 0.88 in the overall scale. After removing these two items, the reliability was significantly improved (Cronbach's alpha=0.88). Therefore, the rest of the items were used to calculate the final anxiety score ranging from 18 to 72, with higher score indicating more symptoms of anxiety.

Statistical analysis

Data analysis included descriptive statistics, bivariate analysis, and hierarchical longitudinal analysis. Descriptive statistics were reported on all the variables used in this study. *Mean* and *standard deviation* (*SD*) were used to describe the continuous variables while *frequencies* and *percentages* were used for categorical variables. Changes of the clinical outcomes and psycho-behavioral factors across the time were tested. Analysis of variance (ANOVA) was used to test the changes of continuous variables while Chi-square test was used for that of categorical variables.

Hierarchical longitudinal analysis was conducted to carry out the research goals. In longitudinal analysis, due to the study design, age, time since HIV diagnosis, duration of ART, employment, BMI, HIV-related stigma, ART self-efficacy, HIV symptom management self-efficacy, depression, anxiety, and ART adherence were used as time-varying variables while gender, marital status, ethnicity, types of residence, education attainment, levels of monthly income, and transmission modes were used as time-invariant variables. Before the multivariable analysis, bivariate analysis was conducted to examine the relationship between each clinical outcome and independent variables using generalized linear mixed model. Crude odds ratio (*OR*) or regression coefficient and 95% confidence intervals (*CI*) were reported in bivariate analysis. Sociodemographic characteristics with *p*-values less than 0.10 were controlled as covariates in multivariable analysis.

In hierarchical longitudinal analysis, for CD4 count and viral suppression, generalized linear mixed model with categorical outcome was employed to examine my hypotheses. First of all, covariates and duration of ART were controlled as confounders in model 1 after adjusting for the repeated measurements. Moreover, psycho-behavioral factors, such as ART self-efficacy, HIV symptom management self-efficacy, ART adherence, depression, and anxiety, were added to model 1 and examined their impacts on the outcomes (model 2). Finally, to examine the impacts of internalized, anticipated, and enacted stigma on outcomes, these three types of stigma were added to model 2 and tested in model 3 simultaneously. As CD4 count and viral suppression were binary outcomes, the distribution was specified as "binomial distribution", and link function was defined as "logit link function". To model the correlations of CD4 count and viral suppression at baseline, 6-, 12-, and 18- month follow-ups, correlation structures (e.g., unstructured covariance, autoregressive covariance, exchangeable covariance, and independent covariance) were examined, and multiple indices (i.e., Queensland Investment Corporation [*QIC*] and *QICu*) were used for evaluating the goodness of fit (Cui & Qian, 2007). Model with the smallest values of the *QIC* and *QICu* was considered as having the best model fit (Cui & Qian, 2007). If the best models selected by *QIC* and *QICu* were inconsistent, *QIC* was used as the final criteria for model selection (Cui & Qian, 2007). Adjusted *OR* (*AOR*) and its 95% *CI* were reported.

In terms of HRQoL, linear mixed effect model was employed. A similar modelling procedure was conducted to examine the impacts of sociodemographic characteristics, psycho-behavioral factors, and HIV-related stigma on HRQoL after adjusting for the repeated measures. Besides the covariates and potential confounders, CD4 count was adjusted in the analysis. Correlation structures were also examined, and Log likelihood value, Akaike Information Criterion [*AIC*], Corrected *AIC* [*AICC*], and Bayes Information Criterion [*BIC*] were used as the indicators for model selection (Fitzmaurice, Laird, & Ware, 2011). Model with smaller *AIC*, *AICC*, *BIC* had better model fit (Fitzmaurice et al., 2011). If the values of these indicators were inconsistent, BIC was used as the final criteria for model selection. Regression coefficient (β) and its 95%*CI* were reported. Pseudo R square (R^2) was reported to evaluate the amount of variance being accounted for in each model (Edwards, Muller, Wolfinger, Qaqish, & Schabenberger, 2008) during the process of hierarchical longitudinal analysis. All the analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

4.4 Results

Descriptive statistics

Table 4.1 shows the sociodemographic characteristics of PLWH at baseline. Among the 1,198 PLWH, the average age at baseline was 39.0 (*SD* = 9.2) years old ranging from 18 to 60. More than half of them were male (771 [64.4%]), married/cohabitated (666 [56.2%]), had less than or equal to middle school education (719 [60.0%]), and/or had full time employment (734 [61.7%]). More than one-third of them were living in a city (536 [44.9%]) and/or had monthly income between 2,000 and 3,999 Yuan (584 [48.9%]).

In regard to the characteristics of HIV infection, the average time since HIV diagnosis and duration of ART treatment were 5.5 (*SD* = 3.1) and 4.8 (*SD* = 3.0) years, respectively. Nearly 70% of them (832 [69.7%]) were infected through sexual activity. There were 94.3% (1,130/1,198) of the PLWH who achieved viral suppression but only 45.1% (540/1,198) of the participants who had their CD4 count equal to or higher than 500 cells/μl. The average score of HRQoL was 73.7 (*SD* = 13.1). There were 80.8% (963/1,192) of the PLWH who had optimal ART adherence.

For psychosocial factors, the average scores of internalized, anticipated, and enacted stigma were 16.3 (*SD* = 5.5), 23.2 (*SD* = 7.7), 0.9 (*SD* = 2.1), respectively. The mean score of ART self-efficacy was 24.5 (*SD* = 5.0), and that of the HIV symptom management self-efficacy was 33.5 (*SD* = 9.1). The averages of depression and anxiety are shown in Table 4.2.

Changes of clinical outcomes and predictors

Across the 6-, 12-, and 18- month follow-ups, study attrition rates were lower than 5.0% (Table 4.2). The changes of clinical outcomes (i.e., viral suppression and HRQoL) were significant except CD4 count. As time increased, the percentage of PLWH who had their CD4 count equal to or higher than 500 cells/µl increased from 45.1% (540/1,198) at baseline to 47.0% (563/1,198) at 18-month follow-up (Figure 4.1). However, this change was not significant ($\chi^2 = 1.23$, $p > 0.05$). Compared with CD4 count, the percentage of PLWH who achieved viral suppression increased from 94.3% (1,130/1,198) to 97.8% (1,135/1,161), and this change was significant ($\chi^2 = 18.16$, $p < 0.01$) (Figure 4.2). Generally, participants' HRQoL significantly decreased over time (Figure 4.3) although the average score showed slight increases at 12-month follow-up.

In terms of the changes in psycho-behavioral factors, all of their changes were statistically significant within the study period. Particularly, internalized (Figure 4.4a) and anticipated (Figure 4.4b) stigma had slight changes at 6- and 12- month follow-ups but decreased at 18- month follow up. Even though there were slight changes in between, the average score of enacted stigma (Figure 4.4c) remained the same at baseline and 18-month follow-up. Both scores of ART self-efficacy (Figure 4.5a) and HIV symptom management self-efficacy (Figure 4.5b) at 18-month follow-up decreased as compared with their baseline scores. The percentage of PLWH with optimal ART adherence (Figure 4.6) increased from 80.8% (963/1,192) at baseline to 85.5% (983/1,150) at 12-month and then decreased to 80.1% at 18-month follow-up. The changes of clinical outcomes and predictors are shown in Table 4.2. Figures 4.7a and 4.7b show the changes of depression and anxiety, respectively.

Clinical outcome: CD4 count

Bivariate analysis

The results of bivariate analyses showed that as age increased, the probability of PLWH with their CD4 count equal to or higher than 500 cells/μl decreased. PLWH who were male, of Han ethnicity, and acquired HIV through sex activity also had lower probability of having their CD4 count equal to or higher than 500 cells/μl. PLWH with longer time since HIV diagnosis had higher probability of higher level of CD4 count while the duration of ART treatment did not show a significant impact. Participants who were single/separated, living in a county or city, had at least high school education, and/or had monthly income at least 4,000 Yuan had higher probability of having their CD4 count equal to or higher than 500 cells/μl. Both ART self-efficacy and HIV symptom management self-efficacy had significant and positive impacts on CD4 count. No significant relationships between HIV-related stigma, optimal ART adherence and CD4 count were found. Table 4.3 shows the detailed results of bivariate analysis of longitudinal CD4 count.

Hierarchical generalized linear mixed model of CD4 count

Hierarchical generalized linear mixed model was conducted to examine the contribution of predictors on the variances in CD4 count. In step 1 (model 1), sociodemographic characteristics with *p*-values less than 0.10 (i.e., age, gender, marital status, ethnicity, types of residence, education attainment, levels of monthly income, transmission modes, BMI) and duration of ART were entered into model 1 after adjusting for repeated measures. In step 2 (model 2), psycho-behavioral factors, such as ART self-efficacy, HIV symptom management self-efficacy, ART adherence, depression, and anxiety, were added to model 1. Finally, internalized, anticipated, and enacted stigma were added to model 2 simultaneously and tested their separate impacts on CD4 count in model 3.

Table 4.4 shows the results of hierarchical generalized linear mixed model of CD4 count. After adjusting for sociodemographic characteristics, duration of ART, and time effect, model 1 explained 12.7% of the variances in outcome. PLWH who were older (*AOR* = 0.71, 95%*CI*: 0.62 ~ 0.81), of Han ethnicity (*AOR* = 0.77, 95%*CI*: 0.62 ~ 0.96), male (*AOR* = 0.60, 95%*CI*: 0.47 ~ 0.77), and/or underweight (*AOR* = 0.57, 95%*CI*: 0.44 ~ 0.73) had lower probability of having their CD4 count equal to or higher than 500 cells/μl. Participants with longer duration of ART treatment (*AOR* = 1.15, 95%*CI*: 1.03 ~ 1.29), living in a county (*AOR* = 1.54, 95%*CI*: 1.14 ~ 2.09) or city (*AOR* = 1.60, 95%*CI*: 1.23 ~ 2.09), and/or those who were overweight/obese (*AOR* = 1.29, 95%*CI*: 1.05 ~ 1.58) had higher probability of having higher levels of CD4 count. No significant relationships between CD4 count and marital status, education attainment, levels of monthly income, and transmission modes were found.

After adding psycho-behavioral factors to the model 1, model 2 explained an additional 3.7% of the variance in CD4 count. In addition to the significant relationships found in model 1, HIV symptom management self-efficacy (*AOR* = 1.17, 95%*CI*: 1.07 ~ 1.28) and anxiety (*AOR* = 1.14, 95%*CI*: 1.01 ~ 1.27) were positively associated with the probability of higher CD4 count. The time effect was significant (*AOR* = 1.05, 95%*CI*: 1.01 ~ 1.09), which meant that as time increased, the probability of PLWH having their CD4 count equal to or higher than 500 cells/μl increased. ART self-efficacy and ART adherence did not show significant impacts on CD4 count over time.

In model 3, internalized, anticipated, and enacted stigma explained an additional 0.6% of the variance in CD4 count. Internalized (*AOR* = 1.00, 95%*CI*: 0.91 ~ 1.10), anticipated (*AOR* = 1.07, 95%*CI*: 0.97 ~ 1.17), and enacted stigma (*AOR* = 0.99, 95%*CI*: 0.91 ~ 1.08) did not show significant impacts on CD4 count. The existing significant relationships between CD4 count and time effect, age, duration of ART, gender, ethnicity, types of residence, BMI, HIV symptom management self-efficacy, and anxiety remained in model 3.

Clinical outcome: Viral suppression

Bivariate analysis

Bivariate analysis of viral suppression was conducted. Living in a city was positively associated with the probability of viral suppression while being infected HIV through sexual activity was negatively related to viral suppression. PLWH with longer time since HIV diagnosis, duration of ART treatment, and higher levels of ART self-efficacy had higher probability of achieving viral suppression. No significant relationships between viral suppression and internalized stigma, anticipated stigma, enacted stigma, HIV symptom management self-efficacy, and ART adherence were found. Results of bivariate analysis of viral suppression were shown in Table 4.5.

Hierarchical generalized linear mixed model of viral suppression

Results of hierarchical generalized linear mixed model of viral suppression showed that model 1 explained 8.9% of the variances in viral suppression. The time effect was statistically significant (*AOR* = 1.28, 95%*CI*: 1.13 ~ 1.46), which meant that as time increased, the probability of achieving viral suppression among PLWH increased. PLWH with longer duration of ART treatment (*AOR* = 1.51, 95%*CI*: 1.18 ~ 1.92) and/or living in a city (*AOR* = 1.68, 95%*CI*: 1.07 ~ 2.64) had higher probability of achieving viral suppression.

After adding psycho-behavioral factors to model 1, model 2 explained an additional 4.6% of variance in viral suppression. Time effect (*AOR* = 1.32, 95%*CI*: 1.16 ~ 1.50) and duration of ART (*AOR* = 1.59, 95%*CI*: 1.23 ~ 2.05) were still significantly associated with viral suppression while the positive impact of living in a city on viral suppression (*AOR* = 1.51, 95%*CI*: 0.93 ~ 2.46) disappeared. PLWH with higher level of ART self-efficacy (*AOR* = 1.29, 95%*CI*: 1.10 ~ 1.51) had higher probability of viral suppression. The relationship between depression and viral suppression was marginally significant (*AOR* = 0.83, 95%*CI*: 0.68 ~ 1.01). No significant relationships between viral suppression and HIV symptom management self-efficacy, anxiety, and ART adherence were found.

In model 3, internalized, anticipated, and enacted stigma explained an additional 1.7% of the variance in viral suppression. In addition to the existing significant relationships in model 2, depression was significantly and negatively associated with the probability of viral suppression (*AOR* = 0.82, 95%*CI*: 0.68 ~ 1.00) in model 3. None of the internalized, anticipated, and enacted stigma had significant impacts on viral suppression. Table 4.6 shows detailed results of hierarchical generalized linear mixed model of viral suppression.

Clinical outcome: HRQoL

Bivariate analysis

Among the sociodemographic characteristics, being divorced/widowed was significantly and negatively associated with HRQoL. PLWH who were living in a city or county, had full time employment, and/or had higher monthly income had better HRQoL as compared to those living in rural areas, without employment, and/or with no more than 1,999 Yuan income each month.

In terms of the HIV-related characteristics, PLWH who were infected through sexual activity had higher levels of HRQoL than those infected through other modes. No significant relationships between HRQoL and time since HIV diagnosis and duration of ART were found.

For the psycho-behavioral factors pertinent to HIV infection, ART self-efficacy, HIV symptom management self-efficacy, and optimal ART adherence were positively related to HRQoL while internalized, anticipated, and enacted stigma were negatively related. Both depression and anxiety showed negative associations with HRQoL. Table 4.7 shows the detailed results of bivariate analysis of HRQoL.

Hierarchical generalized linear mixed model of HRQoL

Hierarchical generalized linear mixed model of HRQoL found that model 1 explained 2.9% of the variance in HRQoL. The time effect on HRQoL was marginally significant (adjusted β = -0.25, 95%*CI*: -0.50 ~ 0.01). PLWH who were living in a city (adjusted β = 2.15, 95%*CI*: 0.80 ~ 3.50) or county (adjusted β = 2.88, 95%*CI*: 1.29 ~ 4.47), had full time employment (adjusted β = 3.01, 95%*CI*: 1.97 ~ 4.05), and/or had higher income (at least 4,000 Yuan: adjusted β = 3.81, 95%*CI*: 2.10 ~ 5.53) had better HRQoL as compared to those living in rural areas, without job, and/or with no more than 1,999 Yuan income each month. PLWH who were infected through sexual activity also had better HRQoL than those infected through other modes (adjusted β = 1.43, 95%*CI*:

0.18 ~ 2.67). As compared to PLWH who were married/cohabited, those who were divorced/widowed had lower HRQoL (adjusted β = -2.60, 95%*CI*: -4.29 ~ -0.91).

After adding psycho-behavioral factors to model 1, model 2 explained an additional 11.9% of variances in HRQoL. However, the significant relationships between HRQoL and living in a city (adjusted β = -0.25, 95%*CI*: -1.02 ~ 0.52) or county (adjusted β = -0.42, 95%*CI*: -1.32 ~ 0.48) disappeared. The impact of time on HRQoL became significant and negative, which meant that as time increased, the HRQoL of PLWH decreased significantly (adjusted β = -0.21, 95%*CI*: -0.40 ~ -0.03). In addition to other significant relationships found in model 1, model 2 found that ART self-efficacy (adjusted β = 1.72, 95%*CI*: 1.45 ~ 2.00), HIV symptom management self-efficacy (adjusted β = 1.16, 95%*CI*: 0.87 ~ 1.44), and optimal ART adherence (adjusted β = 0.63, 95%*CI*: 0.00 ~ 1.26) were positively related to HRQoL while depression (adjusted β = -4.90, 95%*CI*: -5.26 ~ -4.55) and anxiety (adjusted β = -4.06, 95%*CI*: -4.41 ~ -3.70) showed negative effects.

In model 3, internalized, anticipated, and enacted stigma explained an additional 1.0% of the variance in HRQoL. The significant impact of ART adherence on HRQoL disappeared (adjusted β = 0.56, 95%*CI*: -0.06 ~ 1.18). In addition to other significant relationships found in model 2, model 3 found that internalized (adjusted β = -0.78, 95%*CI*: -1.07 ~ -0.49), anticipated (adjusted β = -0.84, 95%*CI*: -1.12 ~ -0.55), and enacted stigma (adjusted β = -0.83, 95%*CI*: -1.10 ~ -0.56) had significant and negative impacts on HRQoL. Table 4.8 shows detailed results of hierarchical generalized linear mixed model of HRQoL.

4.5 Discussion

Using data from a prospective cohort and hierarchical longitudinal approach, this study investigated the relationships between internalized, anticipated, enacted stigma and three clinical outcomes. During the study period, all clinical outcomes had significant changes except CD4 count. The three types of HIV-related stigma could explain additional variance, though small, in clinical outcomes after controlling for sociodemographic characteristics, psycho-behavioral factors, and other confounders. Specifically, significant impacts of internalized, anticipated, and enacted stigma on HRQoL were found, but these impacts were not found for CD4 count and viral suppression. To the best of our knowledge, this was the first study exploring the separate impacts of internalized, anticipated, and enacted stigma on three clinical outcomes from a longitudinal perspective. The findings from this study have implications for future stigma research and stigma reduction intervention.

Over time, participants in the current study who were on ART demonstrated improved immunologic and virologic outcomes but decreased HRQoL. The improvement of CD4 count and viral suppression emphasized the importance of linkage to, engage and retention in HIV treatment and care after HIV diagnosis (Hogg, 2018). Most of the PLWH included in this study reported optimal adherence behaviors, which had significant and positive impacts on immunologic recovery and viral suppression. The possible explanation for the decreased HRQoL among PLWH was that HRQoL is a comprehensive indicator of health quality, which included physical health, psychological health, social functioning, and perception about general health (Ashing-Giwa, 2005; Ruiz Perez et al., 2005; Wu et al., 1997). In addition to immunologic functioning and viral suppression, PLWH still need to cope with drug side effects, comorbidities, HIV-related stigma, and other psychological distress (Andersson et al., 2020; Lazarus et al., 2016; Webster, 2019), which may also undermine their HRQoL.

HIV-related stigma could explain the variance in clinical outcomes and showed significant impact on HRQoL but not on CD4 count and viral suppression. All three types of HIV-related stigma had negative impacts on HRQoL. This finding was consistent with that of previous studies (Logie, Ahmed, Tharao, & Loutfy, 2017; Logie et al., 2018; Rao et al., 2012). The high levels of HIV-related stigma could cause mental health problems and reduce social interaction, social support, and resource access among PLWH, which prevent them from coping well with health issues related to HRQoL and result in decreased HRQoL.

In terms of the non-significant relationships between stigma and CD4 count and viral suppression, there are four possible explanations for these findings. First, as the cohort study was conducted in clinics/hospitals, PLWH might have better immunologic and virologic outcomes as compared to those who did not seek help in clinics/hospitals. Second, only four-wave datasets were used in this study, which might limit the ability to examine the significant associations among variables of interest. Third, some confounders (e.g., CD4 count before ART) which were not controlled in this study might also influence the relationships between HIV-related stigma and CD4 count and viral suppression. Finally, stigma might not influence these two outcomes directly but through psycho-behavioral mechanisms. For instance, a large number of research confirmed the negative impacts of HIV-related stigma on ART adherence which was closely related to CD4 count and viral suppression (Katz et al., 2013; Turan et al., 2017).

Psycho-behavioral factors included in this study could explain large variance in clinical outcomes before adding internalized, anticipated, and enacted stigma to the model. After adding these three types of stigma to the final model, the effects of some psycho-behavioral factors changed, which implied that these factors might be the potential mechanisms underlying HIV-related stigma and clinical outcomes. For instance, the significant impacts of ART adherence on HRQoL disappeared after stigma was added to the final model. PLWH who suffered from higher levels of HIV-related stigma might be less likely to adhere to ART, which in turn could increase viral load, impair their immunologic functioning, and compromise their physical health as well as HRQoL (Abdul Bari, 2017; Alsayed, Sereika, Albrecht, Terry, & Erlen, 2017). What is more, we found that some psycho-behavioral factors had differential impacts on the three clinical outcomes. For instance, viral suppression was significantly related to ART self-efficacy but not to HIV symptom management self-efficacy while the inverse result was found in CD4 count. This might be due to the differences between ART self-efficacy and HIV symptom management self-efficacy. ART self-efficacy captured the confidence of adhering to ART, which has close and direct impact on viral suppression (Risser et al., 2007). In contrast, HIV symptom management self-efficacy captured the confidence of managing HIV-related symptoms, such as drug side effects and disease progression, which were closely associated with immunologic functioning and physical health (Eller et al., 2014; Lorig et al., 2001; Zhou et al., 2020). This finding also implied that the psycho-behavioral mechanisms of HIV-related stigma on clinical outcomes might be different.

Unexpectedly, the current study found that anxiety was positively related to CD4 count. CD4 count, the total numbers of CD4 T-cells in body, represents the immunologic functioning and ability to fight with infections (Center for Disease Control and Prevention [CDC], 2019). Generally, it could be boosted or enhanced by short-term anxiety (Dhabhar, 2014; Hellmuth et al., 2017). Young adults are more likely to have immune activation enhanced by short-term anxiety as younger age is associated with better physical functioning which could enhance the immune system to cope with stressors (Dhabhar, 2014; Hellmuth et al., 2017). In our study, nearly 75% of the PLWH were younger than 45 years old (the bottom line of middle age). We conducted a subgroup analysis and found that the positive relationship between anxiety and CD4 count only existed among PLWH under 45 years old (Appendix B). However, the long-term anxiety could suppress the immune response and increase the susceptibility of chronic diseases (Dhabhar, 2014; Ohman, Bergdahl, Nyberg, & Nilsson, 2007). Additionally, there may be gender difference in the relationship between anxiety and CD4 count as prior research found that female were more likely to experience suboptimal health outcomes than male when suffering from psychological distress (Stevens, Murphy, & McKnight, 2003). The subgroup analysis by gender in the future may provide better explanation on this finding.

The findings in this study have some implications for future research and intervention. From the perspective of research, the large variance in clinical outcomes explained by psycho-behavioral factors indicated that these factors might be the mechanisms underlying HIV-related stigma and clinical outcomes. What is more, the differential impacts of psycho-behavioral factors on the three clinical outcomes implied that the psycho-behavioral mechanisms of stigma on clinical outcomes might be different (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013). These mechanisms are worth future investigation. In terms of intervention design, the differential impacts of HIV-related stigma on the three clinical outcomes implied that stigma interventions should be tailored to each clinical outcome. For instance, as internalized, anticipated, and enacted stigma was negatively associated with HRQoL, stigma reduction intervention, such as HIV-related public health education implemented at both intrapersonal and interpersonal levels (Rao et al., 2019), might be effective in improving HRQoL directly. In contrast, due to the non-significant relationships between HIV-related stigma and CD4 count and viral suppression, stigma reduction interventions may not be enough to improve these two outcomes. To improve immunologic and virologic outcomes effectively, interventions targeting treatment-related self-efficacy, ART adherence, and psychological distress (Areri, Marshall, & Harvey, 2020), such as skill training and stress management, are also very important. Particularly, these interventions should be tailored to some sociodemographic characteristics, such as marital status, types of residence, and age group.

There are some limitations that need to be acknowledged in this study. First, we used self-report measures to capture some of the key factors. Therefore, self-report bias might exist. For instance, due to the social desirability bias, the percentage of optimal ART adherence among PLWH in this study might be overestimated (Stirratt et al., 2015). Second, we only included the three common types of HIV-related stigma used in prior research (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013; Turan et al., 2017). However, other types of HIV-related stigma, such as disclosure concerns and concern with public attitudes toward PLWH (Abdul Bari, 2017; Berger et al., 2001), were not considered in this study. For instance, the measure of internalized stigma was derived from the HIV Stigma Scale which also captures disclosure concerns (Berger et al., 2001). The disclosure concerns may influence clinical outcomes through preventing disclosure behaviors among PLWH and limiting their resource access as well as impeding adherence behaviors (Omarzu, 2000; Qiao, Li, & Stanton, 2013). Third, this study only included some well-investigated psycho-behavioral factors, such as ART self-efficacy, HIV symptom management self-efficacy, ART adherence, depression, and anxiety. However, other psycho-behavioral factors, such as positive coping and avoid coping, may also contribute to clinical outcomes (Ironson et al., 2005). Fourth, only limited percentages of variance in clinical outcomes explained by the independent variables. This might be due to some confounders which were not controlled in the analysis. Future research considering more potential confounders are needed. Fifth, PLWH in this study were recruited from the hospitals/clinics. Therefore, they might have better clinical outcomes and lower HIV-related stigma as compared to those who did not seek help in the healthcare settings, which might influence the relationship between stigma and clinical outcomes. Finally, as the participants were recruited from Guangxi, China, cautions are needed when generalizing the findings from this study to other areas in China or other cultural settings.

4.6 Conclusion

HIV-related stigma could explain additional information of clinical outcomes and show different impacts. Future studies are called for investigating the psycho-behavioral mechanisms of HIV-related stigma on clinical outcomes. To improve clinical outcomes among PLWH effectively, interventions are warrant to not only target HIV-related stigma at both intrapersonal and interpersonal levels but also to promote resilience which could alleviate the negative impacts of HIV-related stigma.

4.7 References

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Table 4.1 Sociodemographic characteristics of PLWH at baseline assessment

Variables	**Missing data (%)**	**N (%)**
Sample size	-	1,198 (100.0)
Age in years (*Mean*, *SD*)	0 (0.0)	39.0 (±9.2)
Time since HIV diagnosis in years (*Mean*, *SD*)	0 (0.0)	5.5 (±3.1)
Duration of ART in years (*Mean*, *SD*)	66 (5.5)	4.8 (±3.0)
Gender	0 (0.0)	
Male		771 (64.4)
Female		427 (35.6)
Marriage	12 (1.0)	
Single/separated		360 (30.4)
Married/cohabitated		666 (56.2)
Divorced/widowed		160 (13.4)
Ethnicity	1 (0.0)	
Han		778 (65.0)
Non-Han		419 (35.0)
Types of residence	3 (0.0)	
City		536 (44.9)
County		231 (19.3)
Rural		428 (35.8)
Education attainment	0 (0.0)	
Less than or equal to middle school		719 (60.0)
High school or above		479 (40.0)
Employment	9 (0.8)	
Unemployed		220 (18.5)
Part time		235 (19.8)
Full time		734 (61.7)
Levels of monthly income	3 (0.0)	
No more than 1,999 Yuan		370 (31.0)

2,000 ~ 3,999 Yuan		584 (48.9)
At least 4,000 Yuan		241 (20.2)
Transmission modes	5 (0.4)	
Sexual activity		832 (69.7)
Others		361 (30.3)
Body Mass Index	0 (0.0)	
Underweight		161 (13.4)
Normal/healthy weight		873 (72.9)
Overweight/obese		164 (13.7)

Table 4.2 Changes of clinical outcomes and predictors among PLWH

Variables	**Baseline**	**6-month**	**12-month**	**18-month**	χ^2/ ***F*** **values**
Sample sizes (*n*, %)	1,198 (100.0)	1,197 (99.9)	1,163 (97.1)	1,161 (96.9)	-
Attrition rates (*n*, %)	-	1 (0.1)	35 (2.9)	37 (3.1)	-
Clinical outcomes					
CD4 count (*n*, %)					1.23^{a}
Less than 500 cells/µl	658 (54.9)	657 (54.8)	656 (54.8)	635 (53.0)	
500 cells/µl or more	540 (45.1)	541 (45.2)	542 (45.2)	563 (47.0)	
Viral suppression (*n*, %)					**18.16^{a***}**
Yes	1,130 (94.3)	1,145 (95.8)	1,109 (95.4)	1,135 (97.8)	
No	68 (5.7)	50 (4.2)	54 (4.6)	26 (2.2)	
Health-related quality of life (*Mean*, *SD*)	73.7 (±13.1)	71.2 (±13.4)	74.0 (±12.4)	72.1 (±13.3)	**11.50^{b***}**
Predictors					
Internalized stigma (*Mean*, *SD*)	16.3 (±5.5)	17.0 (±5.0)	15.5 (±4.7)	16.0 (±5.1)	**18.28^{b***}**
Anticipated stigma (*Mean*, *SD*)	23.2 (±7.7)	22.6 (±7.2)	21.2 (±6.8)	22.0 (±7.1)	**15.89^{b***}**
Enacted stigma (*Mean*, *SD*)	0.9 (±2.1)	0.8 (±2.2)	0.4 (±1.3)	0.9 (±1.3)	**16.41^{b***}**
ART self-efficacy (*Mean*, *SD*)	24.5 (±5.0)	23.7 (±5.0)	24.5 (±5.0)	24.2 (±5.3)	**6.08^{b***}**
HIV symptom management self-efficacy (*Mean*, *SD*)	33.5 (±9.1)	34.1 (±7.5)	34.2 (±7.6)	32.6 (±8.5)	**9.94^{b***}**
Depression (*Mean*, *SD*)	6.6 (±4.7)	7.5 (±5.0)	7.0 (±4.7)	7.1 (±5.0)	**7.45^{b***}**
Anxiety (*Mean*, *SD*)	26.9 (±6.4)	27.5 (±6.9)	25.7 (±6.0)	27.3 (±6.7)	**18.24^{b***}**
ART adherence (*n*, %)					**13.38^{b**}**
Optimal	963 (80.8)	981 (82.2)	983 (85.5)	928 (80.1)	
Suboptimal	229 (19.2)	213 (17.8)	167 (14.5)	230 (19.9)	

Note: *SD*: Standard deviation; *a*: Chi-square test; *b*: ANOVA; **: $p < 0.01$; ***: $p < 0.001$.

Table 4.3 Bivariate analysis of longitudinal CD4 count

Variables	CD4 count (< 500 cells/µl vs. ≥ 500 cells/µl) *Crude OR* (95%*CI*)	*p*-value
Age in years	0.96 (0.95~0.97)	<0.001***
Time since HIV diagnosis in years	1.04 (1.01~1.07)	0.011*
Duration of ART in years	1.01 (0.98~1.05)	0.421
Gender		<0.001***
Male	0.72 (0.59~0.88)	
Female	Reference	
Marital status		0.006**
Single/separated	1.36 (1.10~1.70)	
Married/cohabitated	Reference	
Divorced/widowed	0.88 (0.65~1.18)	
Ethnicity		
Han	0.81 (0.66~0.99)	0.044*
Non-Han	Reference	
Types of residence		<0.001***
City	2.18 (1.74~2.73)	
County	1.78 (1.35~2.35)	
Rural	Reference	
Education attainment		<0.001***
Less than or equal to middle school	Reference	
High school or above	1.64 (1.34~2.00)	
Employment		0.107
Unemployed	Reference	
Part time	0.93 (0.73~1.19)	
Full time	1.13 (0.91~1.41)	

Levels of monthly income		**<0.001******
No more than 1,999 RMB	Reference	
2,000 ~ 3,999 RMB	1.06 (0.85~1.33)	
At least 4,000 RMB	1.81 (1.37~2.39)	
Transmission modes		**0.041***
Sexual activity	0.80 (0.64~0.99)	
Others	Reference	
Body Mass Index		0.070
Underweight	0.87 (0.68~1.12)	
Normal/healthy weight	Reference	
Overweight/obese	1.30 (0.99~1.70)	
Internalized stigma	0.99 (0.98~1.01)	0.299
Anticipated stigma	1.00 (0.99~1.01)	0.962
Enacted stigma	0.98 (0.95~1.02)	0.309
ART self-efficacy	1.02 (1.01~1.04)	**0.009****
HIV symptom management self-efficacy	1.03 (1.02~1.04)	**0.001*****
Depression	0.99 (0.98~1.01)	0.222
Anxiety	1.00 (0.99~1.01)	0.787
ART adherence (*n*, %)		0.644
Optimal	0.96 (0.80~1.15)	
Suboptimal	Reference	

Note: *OR*: Odds ratio; *CI*: Confidence interval; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 4.4 Hierarchical generalized linear mixed model of CD4 count

Variables	***AOR* (95% *CI*)**		
	Model 1 (*n*=1,119)	**Model 2 (*n*=1,073)**	**Model 3 (*n*=1,066)**
Step 1: Sociodemographic characteristics			
Time	1.04 (1.00~1.08)	**1.05 (1.01~1.09)***	**1.05 (1.01~1.09)***
Age in years	**0.71 (0.62~0.81)*****	**0.72 (0.63~0.83)*****	**0.72 (0.63~0.83)*****
Duration of ART in years	**1.15 (1.03~1.29)***	**1.18 (1.05~1.32)****	**1.18 (1.05~1.33)****
Gender			
Male	**0.60 (0.47~0.77)*****	**0.59 (0.46~0.76)*****	**0.59 (0.46~0.76)*****
Female		Reference	
Marital status			
Single/separated	1.21 (0.90~1.62)	1.22 (0.91~1.64)	1.21 (0.90~1.63)
Married/cohabitated		Reference	
Divorced/widowed	0.87 (0.62~1.21)	0.88 (0.63~1.23)	0.88 (0.63~1.24)
Ethnicity			
Han	**0.77 (0.62~0.96)***	**0.77 (0.62~0.96)***	**0.77 (0.62~0.96)***
Non-Han		Reference	
Types of residence			
City	**1.60 (1.23~2.09)*****	**1.52 (1.16~1.98)****	**1.52 (1.16~1.99)****
County	**1.54 (1.14~2.09)****	**1.47 (1.08~2.00)***	**1.47 (1.08~2.01)***
Rural		Reference	
Education attainment			
Less than or equal to middle school		Reference	
High school or above	1.27 (0.98~1.64)	1.24 (0.96~1.61)	1.23 (0.95~1.59)
Levels of monthly income			
No more than 1,999 Yuan		Reference	
2,000 ~ 3,999 Yuan	1.10 (0.86~1.41)	1.09 (0.85~1.40)	1.08 (0.84~1.39)
At least 4,000 Yuan	1.34 (0.97~1.85)	1.31 (0.94~1.82)	1.28 (0.92~1.78)

Transmission modes			
Sexual activity	1.04 (0.82~1.32)	0.85 (0.66~1.08)	0.85 (0.66~1.09)
Others		Reference	
Body Mass Index			
Underweight	**0.57 (0.44~0.73)*****	**0.75 (0.57~0.99)***	**0.75 (0.57~1.00)***
Normal/healthy weight		Reference	
Overweight/obese	**1.29 (1.05~1.58)***	**1.39 (1.04~1.87)***	**1.39 (1.04~1.87)***
Step 2: Psycho-behavioral factors			
ART self-efficacy	-	1.00 (0.91~1.09)	1.00 (0.92~1.09)
HIV symptom management self-efficacy	-	**1.17 (1.07~1.28)*****	**1.19 (1.08~1.30)*****
Depression	-	0.94 (0.84~1.05)	0.92 (0.82~1.04)
Anxiety	-	**1.14 (1.01~1.27)***	**1.14 (1.01~1.28)***
ART adherence (*n*, %)	-		
Optimal	-	0.99 (0.81~1.20)	0.97 (0.80~1.19)
Suboptimal	-	Reference	
Step 3: HIV-related stigma			
Internalized stigma	-	-	1.00 (0.91~1.10)
Anticipated stigma	-	-	1.07 (0.97~1.17)
Enacted stigma	-	-	0.99 (0.91~1.08)
Pseudo R^2	0.127	0.164	0.170
ΔR^2	-	0.037	0.006

Note: *AOR*: Adjusted odds ratio; *CI*: Confidence interval; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 4.5 Bivariate analysis of longitudinal viral suppression

Variables	Viral suppression (Yes vs. No) *Crude OR* (95%*CI*)	*p*-value
Age in years	0.97 (0.80~1.17)	0.729
Time since HIV diagnosis in years	1.39 (1.10~1.74)	**0.006****
Duration of ART in years	1.18 (1.09, 1.28)	**<0.001*****
Gender		0.962
Male	0.99 (0.65~1.51)	
Female	Reference	
Marital status		0.835
Single/separated	0.88 (0.56~1.37)	
Married/cohabitated	Reference	
Divorced/widowed	0.91 (0.49~1.68)	
Ethnicity		0.244
Han	1.28 (0.85~1.93)	
Non-Han	Reference	
Types of residence		0.079
City	1.59 (1.01~2.51)	
County	1.13 (0.66~1.94)	
Rural	Reference	
Education attainment		0.108
Less than or equal to middle school	Reference	
High school or above	1.42 (0.93~2.19)	
Employment		0.712
Unemployed	Reference	
Part time	1.11 (0.72~1.70)	
Full time	0.96 (0.68~1.36)	

Levels of monthly income		0.726
No more than 1,999 RMB	Reference	
2,000 ~ 3,999 RMB	0.83 (0.52~1.32)	
At least 4,000 RMB	0.88 (0.49~1.58)	
Transmission modes		**0.031***
Sexual activity	0.60 (0.38~0.96)	
Others	Reference	
Body Mass Index		0.545
Underweight	1.30 (0.75~2.26)	
Normal/healthy weight	Reference	
Overweight/obese	0.89 (0.53~1.50)	
Internalized stigma	1.02 (0.88~1.18)	0.785
Anticipated stigma	1.03 (0.90~1.18)	0.688
Enacted stigma	0.96 (0.88~1.05)	0.359
ART self-efficacy	1.04 (1.01~1.07)	**0.011***
HIV symptom management self-efficacy	1.01 (0.99~1.03)	0.161
Depression	0.90 (0.78~1.03)	0.118
Anxiety	0.97 (0.80~1.17)	0.729
ART adherence (*n*, %)		0.685
Optimal	0.93 (0.64~1.34)	
Suboptimal	Reference	

Note: *OR*: Odds ratio; *CI*: Confidence interval; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 4.6 Hierarchical generalized linear mixed model of viral suppression

Variables	***AOR* (95% *CI*)**		
	Model 1 (*n*=1,108)	**Model 2 (*n*=1,080)**	**Model 3 (*n*=1,073)**
Step 1: Sociodemographic characteristics			
Time	**1.28 (1.13~1.46)*****	**1.32 (1.16~1.50)*****	**1.31 (1.15~1.49)*****
Duration of ART in years	**1.51 (1.18~1.92)*****	**1.59 (1.23~2.05)*****	**1.58 (1.22~2.04)*****
Transmission modes			
Sexual activity	0.70 (0.44~1.13)	0.68 (0.42~1.10)	0.70 (0.43~1.13)
Others		Reference	
Types of Residence			
City	**1.68 (1.07~2.64)***	1.51 (0.93~2.46)	1.53 (0.94~2.51)
County	1.21 (0.71~2.08)	1.24 (0.72~2.16)	1.29 (0.73~2.26)
Rural		Reference	
Step 2: Psycho-behavioral factors			
ART self-efficacy	-	**1.29 (1.10~1.51)****	**1.32 (1.12~1.55)*****
HIV symptom management self-efficacy	-	1.06 (0.89~1.26)	1.07 (0.90~1.28)
Depression	-	0.83 (0.68~1.01)†	**0.82 (0.68~1.00)***
Anxiety	-	1.23 (0.99~1.54)	1.21 (0.96~1.53)
ART adherence (*n*, %)	-		
Optimal	-	0.82 (0.54~1.25)	0.76 (0.49~1.17)
Suboptimal		Reference	
Step 3: HIV-related stigma			
Internalized stigma	-	-	0.98 (0.84~1.13)
Anticipated stigma	-	-	1.12 (0.94~1.33)
Enacted stigma	-	-	1.06 (0.92~1.23)
Pseudo R^2	0.089	0.135	0.152
ΔR^2	-	0.046	0.017

Note: *AOR*: Adjusted odds ratio; *CI*: Confidence interval; †: Marginal significance ($0.05 \leq p \leq 0.06$); *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 4.7 Bivariate analysis of longitudinal health-related quality of life

Variables	**Health-related Quality of Life** **Crude *β* (95%*CI*)**	***p*-value**
Sociodemographic characteristics		
Age in years	-0.31 (-0.88~0.27)	0.266
Time since HIV diagnosis in years	-0.18 (-0.76~0.39)	0.533
Duration of ART in years	-0.13 (-0.72~0.46)	0.661
Gender		
Male	0.53 (-0.66~1.73)	0.383
Female	Reference	
Marital status		**0.004****
Single/separated	0.47 (-0.83~1.76)	
Married/cohabitated	Reference	
Divorced/widowed	-2.62 (-4.36~-0.88)	
Ethnicity		0.532
Han	-0.38 (-1.59~0.82)	
Non-Han	Reference	
Types of residence		**<0.001*****
City	2.91 (1.63~4.18)	
County	2.98 (1.37~4.58)	
Rural	Reference	
Education attainment		0.407
Less than or equal to middle school	Reference	
High school or above	0.50 (-0.68~1.67)	
Employment		**<0.001*****
Unemployed	Reference	
Part time	-0.86 (-2.02~0.30)	
Full time	3.28 (2.26~4.30)	

Levels of monthly income		**<0.001*****
No more than 1,999 RMB	Reference	
2,000 ~ 3,999 RMB	1.61 (0.32~2.90)	
At least 4,000 RMB	5.76 (4.15~7.37)	
Transmission modes		**0.002****
Sexual activity	1.96 (0.71~3.20)	
Others	Reference	
Body Mass Index		0.310
Underweight	-0.41 (-1.72~0.91)	
Normal/healthy weight	Reference	
Overweight/obese	0.91 (-0.42~2.24)	
Predictors		
Internalized stigma	-4.85 (-5.19~-4.51)	**<0.001*****
Anticipated stigma	-4.22 (-4.56~-3.87)	**<0.001*****
Enacted stigma	-4.48 (-4.81~-4.15)	**<0.001*****
ART self-efficacy	5.02 (4.68~5.36)	**<0.001*****
HIV symptom management self-efficacy	4.43 (4.07~4.79)	**<0.001*****
Depression	-8.74 (-9.01~-8.48)	**<0.001*****
Anxiety	-8.56 (-8.85~-8.28)	**<0.001*****
ART adherence (*n*, %)		
Optimal	4.42 (3.53~5.30)	**<0.001*****
Suboptimal	Reference	
CD4 count (*n*, %)		0.068
Less than 500 cells/µl	Reference	
500 cells/µl or more	0.80 (-0.06~1.66)	

Note: *CI*: Confidence interval; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 4.8 Hierarchical generalized linear mixed model of health-related quality of life

Variables	**Adjusted *β* (95%CI)**		
	Model 1 (*n*=1,113)	**Model 2 (*n*=1,090)**	**Model 3 (*n*=1,083)**
Step 1: Sociodemographic characteristics			
Time	-0.25 (-0.51~0.01)†	**-0.21 (-0.40~-0.03)***	**-0.19 (-0.37~0.00)***
Age	0.62 (-0.03~1.27)	-0.19 (-0.56~0.18)	-0.07 (-0.43~0.30)
Time since HIV diagnosis	-0.02 (-0.60~0.57)	-0.19 (-0.52~0.14)	-0.17 (-0.50~0.15)
Marital status			
Single/separated	-0.50 (-1.94~0.95)	-0.42 (-1.23~0.39)	-0.38 (-1.19~0.43)
Married/cohabitated		Reference	
Divorced/widowed	**-2.60 (-4.29~-0.91)****	**-1.17 (-2.12~-0.22)***	**-1.27 (-2.21~-0.33)****
Types of residence			
City	**2.15 (0.80~3.50)****	-0.25 (-1.02~0.52)	-0.13 (-0.89~0.64)
County	**2.88 (1.29~4.47)*****	-0.42 (-1.32~0.48)	-0.17 (-1.06~0.72)
Rural		Reference	
Employment			
Unemployed		Reference	
Part time	-0.92 (-2.08~0.26)	-0.29 (-1.08~0.50)	-0.28 (-1.07~0.50)
Full time	**3.01 (1.97~4.05)*****	**1.82 (1.12~2.51)*****	**1.87 (1.18~2.56)*****
Levels of monthly income			
No more than 1,999 RMB		Reference	
2,000 ~ 3,999 RMB	0.69 (-0.62~2.01)	**0.52 (0.11~1.59)***	**0.77 (0.03~1.51)***
At least 4,000 RMB	**3.81 (2.10~5.53)*****	**1.15 (0.18~2.12)***	**1.19 (0.23~2.16)***
Transmission modes			
Sexual activity	**1.43 (0.18~2.67)***	**0.87 (0.17~1.57)***	**0.84 (0.15~1.54)***
Others		Reference	

CD4 count			
Less than 500 cells/µl	0.51 (-0.36~1.38)	0.28 (-0.28~0.83)	0.33 (-0.22~0.88)
500 cells/µl or above		Reference	
Step 2: Psycho-behavioral factors			
ART self-efficacy	**-**	**1.72 (1.45~2.00)*****	**1.49 (1.21~1.77)*****
HIV symptom management self-efficacy	**-**	**1.16 (0.87~1.44)*****	**0.83 (0.54~1.12)*****
Depression	**-**	**-4.90 (-5.26~-4.55)*****	**-4.32 (-4.68~-3.96)*****
Anxiety	**-**	**-4.06 (-4.41~-3.70)*****	**-3.83 (-4.19~-3.48)*****
ART adherence (*n*, %)	**-**		
Optimal	**-**	**0.63 (0.00~1.26)***	0.56 (-0.06~1.18)
Suboptimal		Reference	
Step 3: HIV-related stigma			
Internalized stigma	-	-	**-0.78 (-1.07~-0.49)*****
Anticipated stigma	-	-	**-0.84 (-1.12~-0.55)*****
Enacted stigma	-	-	**-0.83 (-1.10~-0.56)*****
Pseudo R^2	0.029	0.148	0.158
ΔR^2	-	0.119	0.010

Note: *CI*: Confidence interval; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

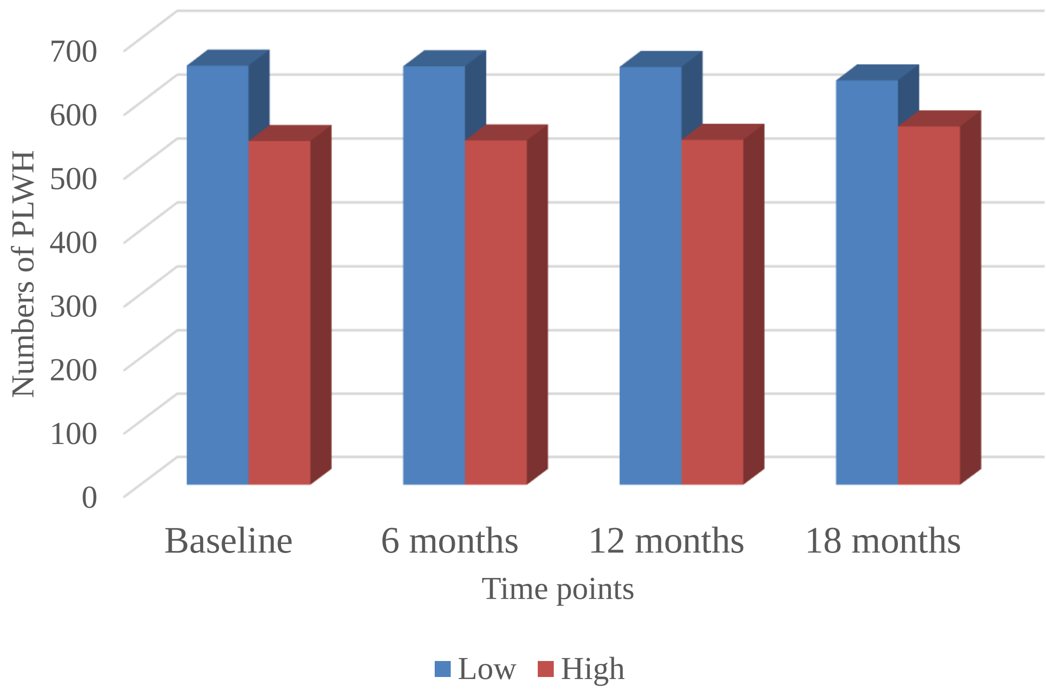


Figure 4.1 Change of CD4 count among PLWH

Note: PLWH: People living with HIV; Low: CD4 count less than 500 copies/μl; High: CD4 count equal to or higher than 500 copies/μl.

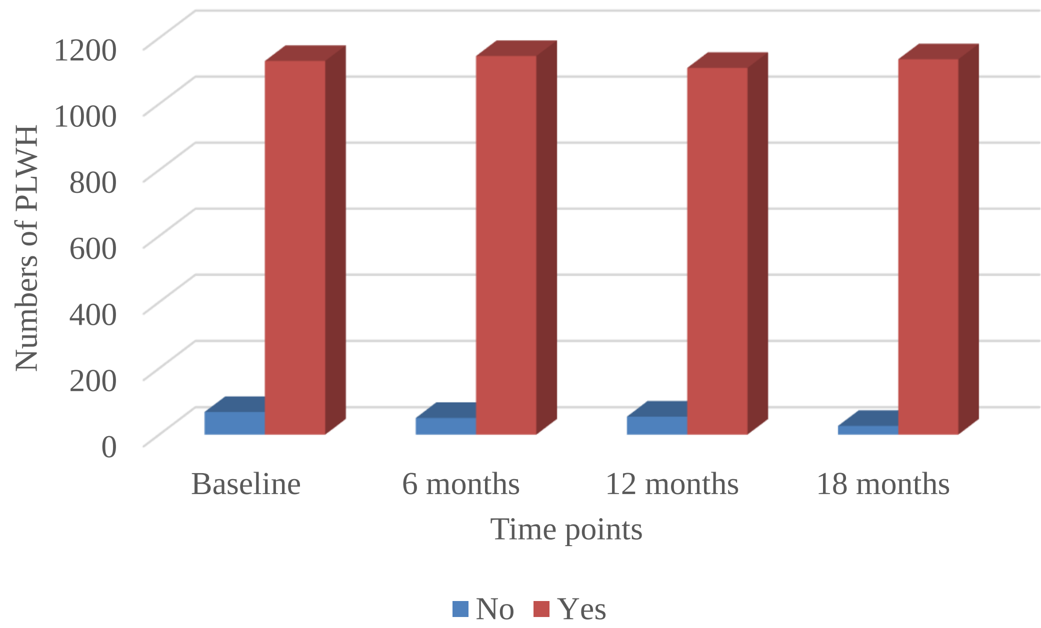


Figure 4.2 Change of viral suppression among PLWH

Note: PLWH: People living with HIV; No: Viral non-suppressed; Yes: Viral suppressed.

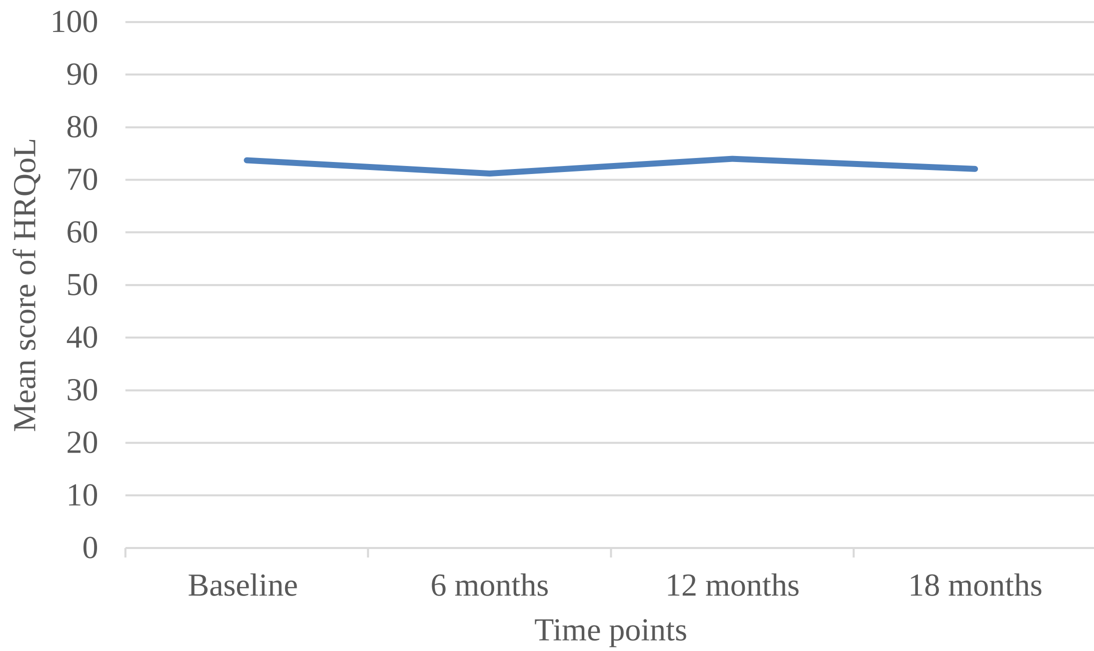
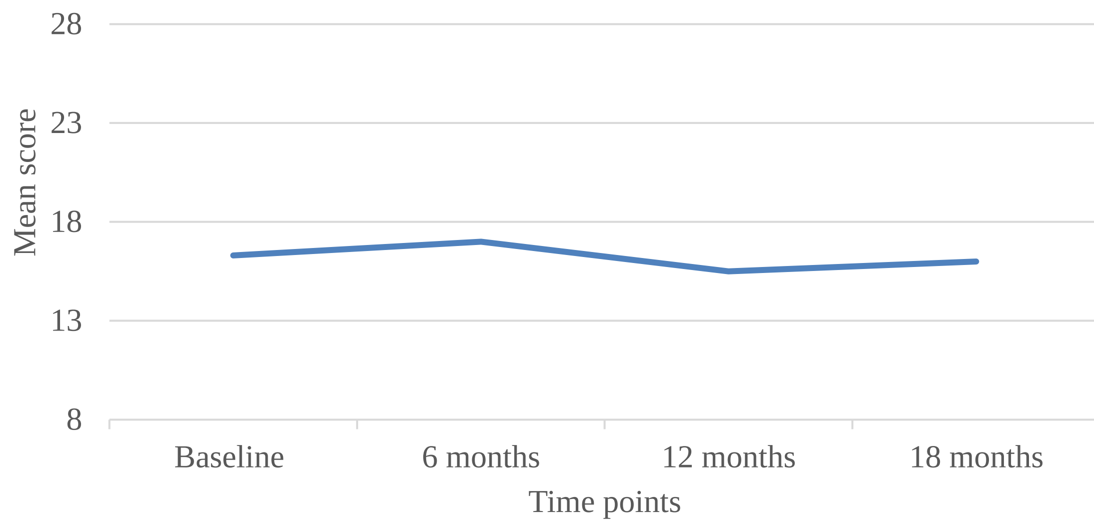
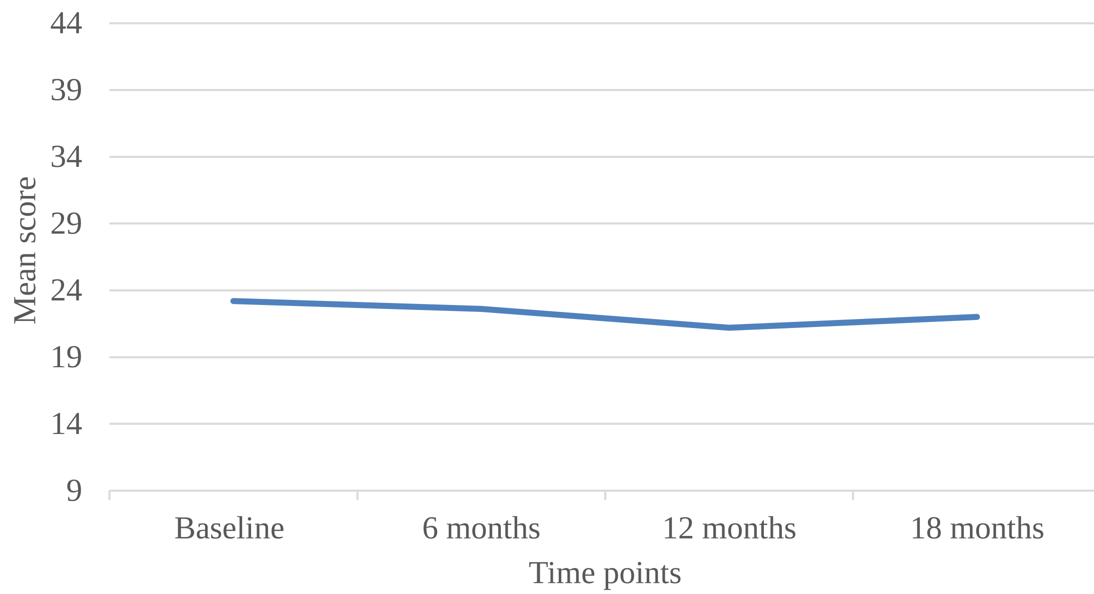


Figure 4.3 Change of HRQoL among PLWH

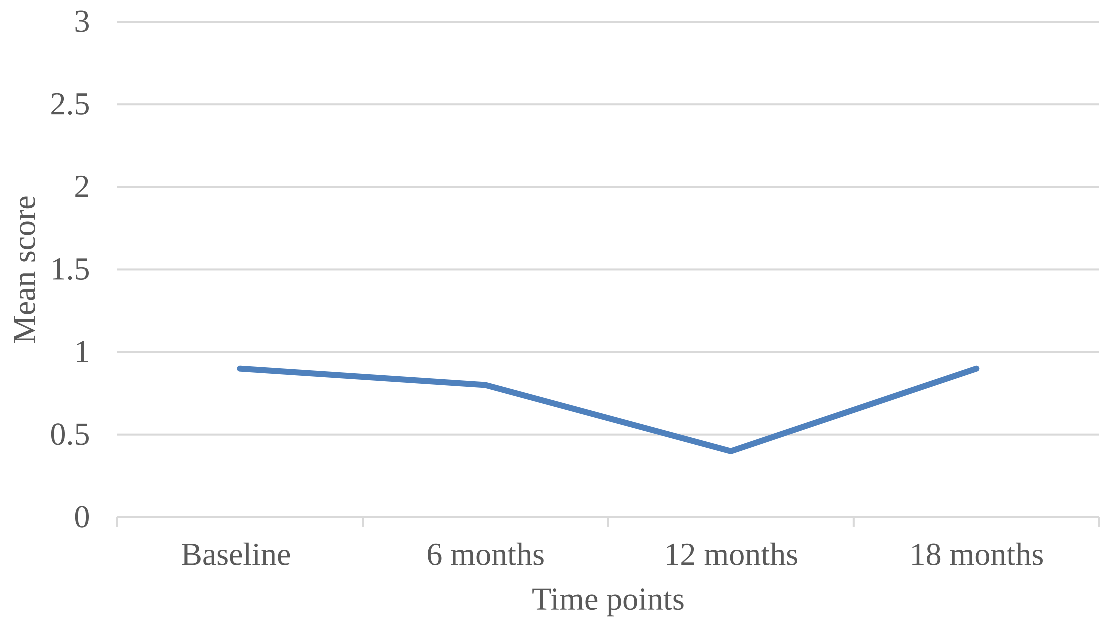
Note: PLWH: People living with HIV; HRQoL: Health-related quality of life.



(a) Internalized stigma



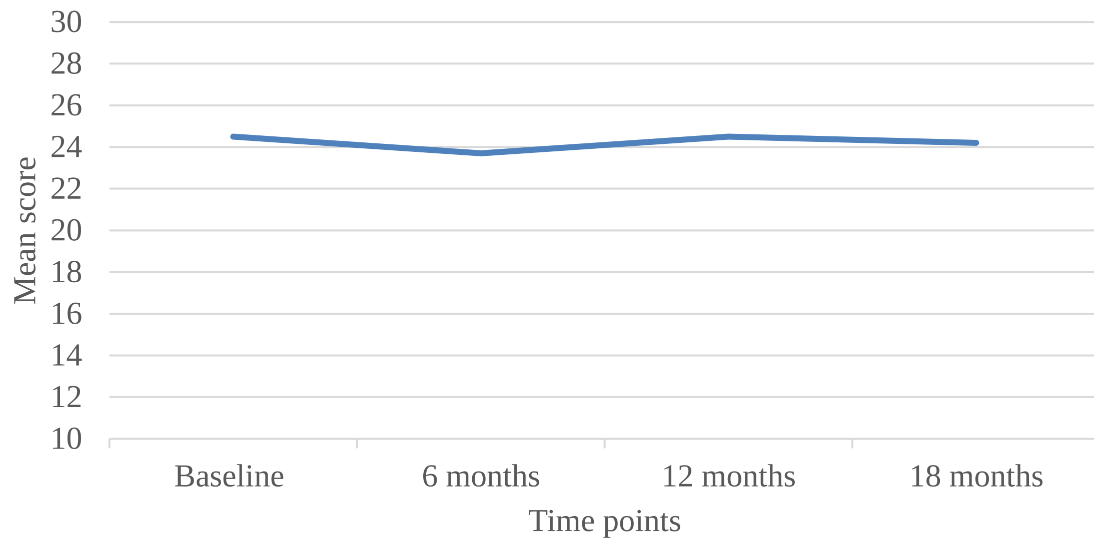
(b) Anticipated stigma



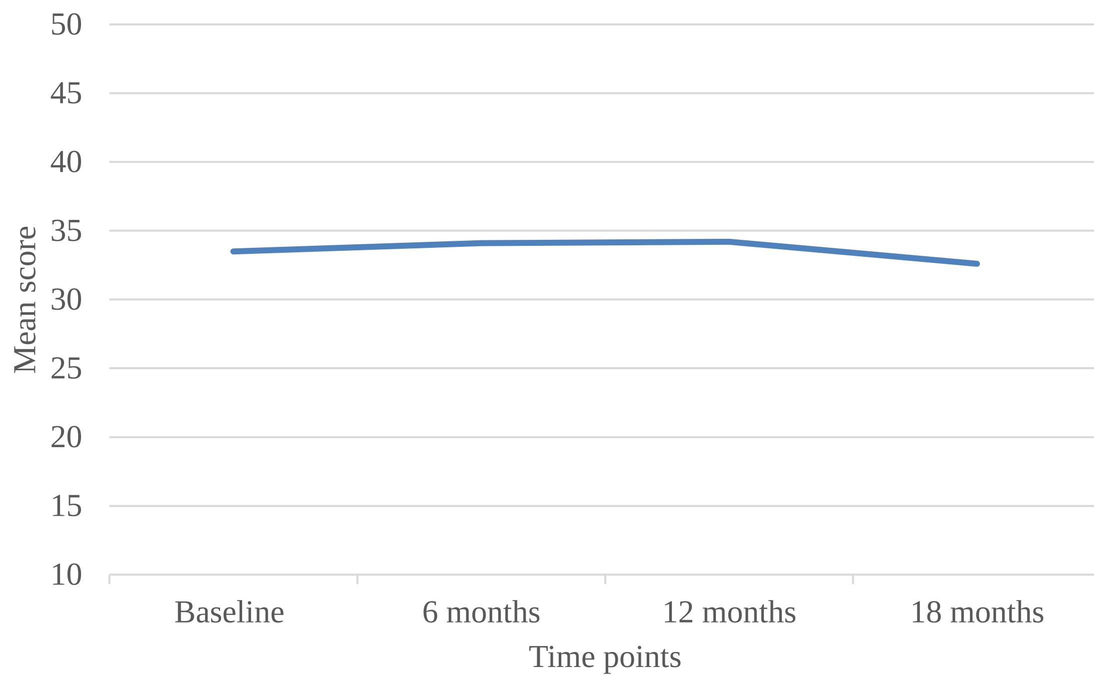
(c) Enacted stigma

Figure 4.4 Changes of internalized, anticipated, and enacted stigma among PLWH

Note: PLWH: People living with HIV.



(a) ART self-efficacy



(b) HIV symptom management self-efficacy

Figure 4.5 Changes of treatment-related self-efficacy among PLWH

Note: PLWH: People living with HIV.

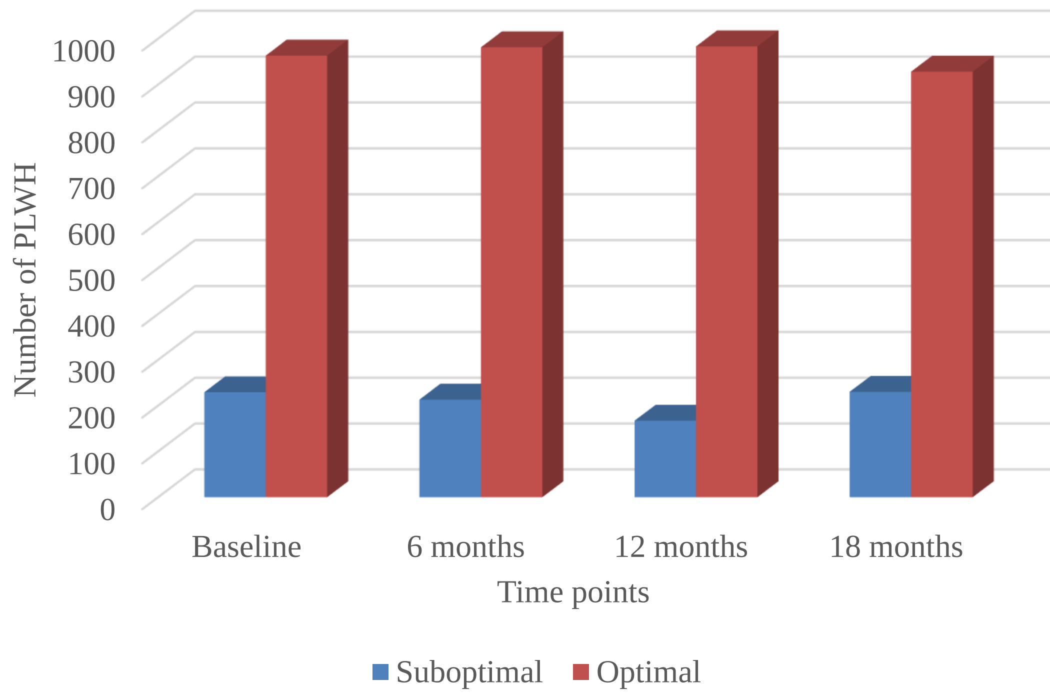
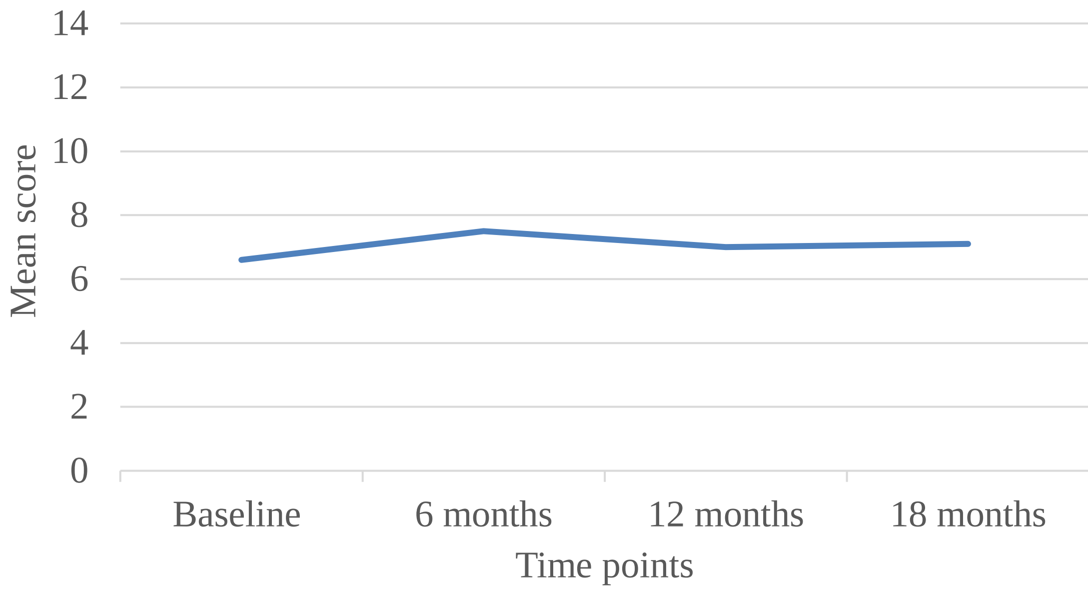
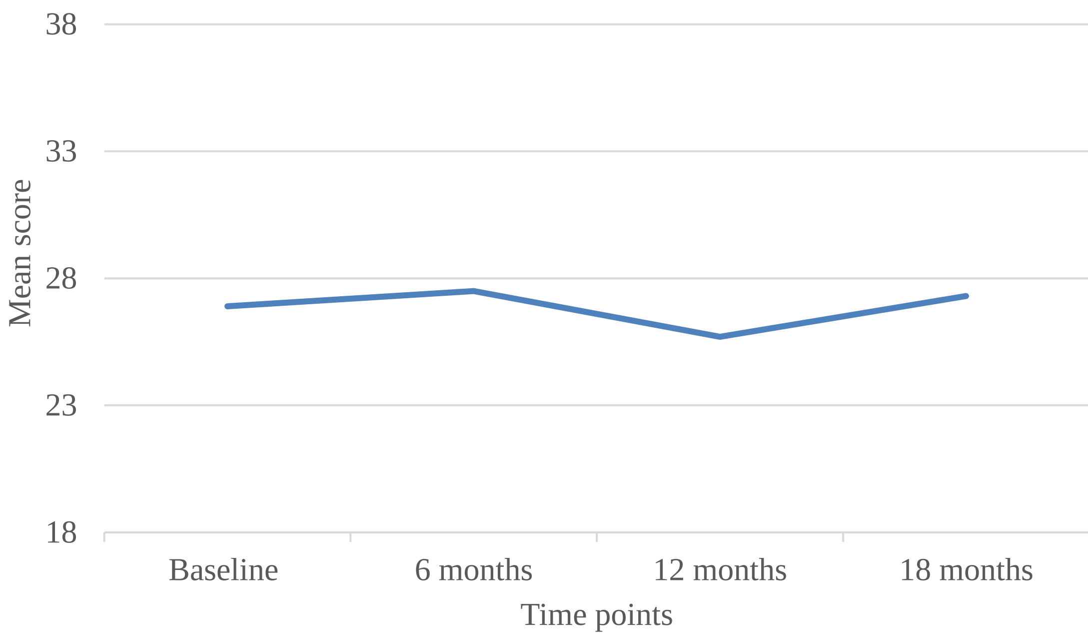


Figure 4.6 Change of ART adherence among PLWH

Note: PLWH: People living with HIV.



(a) Depression



(b) Anxiety

Figure 4.7 Changes of psychological distress among PLWH

Note: PLWH: People living with HIV.

CHAPTER 5

LONGITUDINAL PSYCHO-BEHAVIORAL MECHANISMS OF INTERNALIZED, ANTICIPATED, AND ENACTED STIGMA ON CLINICAL OUTCOMES AMONG PLWH: A PROSPECTIVE COHORT STUDY

5.1 Abstract

Prior research suggested the different mechanisms of internalized, anticipated, and enacted stigma on clinical outcomes among people living with HIV (PLWH). However, currently few studies examined these mechanisms from a longitudinal perspective, especially for those from resource-limited settings. Based on the Health Stigma Framework, this study leveraged data from a prospective cohort and longitudinal mediation analysis to test the psycho-behavioral mechanisms of HIV-related stigma on clinical outcomes among PLWH in Guangxi, China.

Data were derived from a prospective cohort among PLWH which was conducted in Guangxi, China. The primary outcomes were CD4 count, viral suppression, and health-related quality of life (HRQoL). Latent growth curve modelling was employed to test the mediating effects of psycho-behavioral factors (i.e., ART self-efficacy, HIV symptom management self-efficacy, ART adherence) between each type of stigma and clinical outcomes.

None of the three types of stigma had direct impacts on CD4 count and viral suppression, but the direct impacts of internalized (β = -0.184, 95% Confidence Interval [CI]: -0.264 ~ -0.104) and enacted stigma (β = -0.302, 95% CI: -0.431 ~ -0.173) were found in HRQoL. ART self-efficacy, HIV symptom management self-efficacy, and ART adherence could mediate the indirect pathways from HIV-related stigma to viral suppression but these effects were not found for CD4 count. ART self-efficacy could consistently mediate the impacts of the three types of stigma on HRQoL but the mediating effect of HIV symptom management self-efficacy was only found in the pathway between anticipated stigma and HRQoL (β = -0.062, 95% CI: -0.086 ~ -0.037). Across the three types of HIV-related stigma, ART self-efficacy could consistently mediate their impacts on ART adherence. Similarly, only anticipated stigma could affect ART adherence through reducing HIV symptom management self-efficacy (β = -0.005, 95% CI: -0.010 ~ 0.000).

The psycho-behavioral mechanisms were different by different types of HIV-related stigma and clinical outcomes. Future stigma research should consider the characteristics of each type of HIV-related stigma and clinical outcomes and use the relevant theoretical knowledge to frame the pathways between them. Interventions aiming to improve clinical outcomes should be tailored to internalized, anticipated, and enacted stigma and target the relevant psycho-behavioral pathways.

5.2 Introduction

HIV-related stigma refers to devaluing, shaming, and prejudice towards people living with HIV (PLWH) (Chollier, Tomkinson, & Philibert, 2016; Herek, 2016). Stigma is a major barrier to efforts to control the global HIV epidemic. As a social phenomenon, HIV-related stigma exists when labeling, stereotype, and discrimination occur in a power structure (Earnshaw & Chaudoir, 2009; Earnshaw, Smith, Chaudoir, Amico, & Copenhaver, 2013). It could induce social inequalities and influence the health of PLWH. A large body of evidence has demonstrated that HIV-related stigma is closely associated with psychological distress and risk behaviors (Logie & Gadalla, 2009; Tavakkoli et al., 2014), and it is also an impediment to disclosure, treatment adherence, and healthcare access (Chollier et al., 2016; Katz et al., 2013; Sweeney & Vanable, 2016). These negative impacts impair the psychological and physical wellbeing of PLWH.

Clinical outcomes, such as CD4 count, viral load, and health-related quality of life (HRQoL), are important indicators for evaluating treatment efficacy, as well as psychological and physical wellbeing of PLWH. CD4 count and viral load are critical indictors reflecting immunologic functioning and viral suppression (Bentwich, 2005; Marsh et al., 2019). Low CD4 count and high viral load speed up the disease progression and increase the risk of opportunistic infection in PLWH. PLWH who have normal immunologic functioning and who have achieved viral suppression still need to cope with other challenges, such as psychological distress, potential side effect of antiretroviral therapy (ART), and comorbidities. Therefore, HRQoL is a comprehensive construct reflecting health quality (Andersson et al., 2020; Lazarus et al., 2016; Webster, 2019). It assesses the disease burden across four main dimensions including psychological health, physical health, social functioning, and perception about general health (Ashing-Giwa, 2005; Ruiz Perez et al., 2005; Wu, Hays, Kelly, Malitz, & Bozzette, 1997).

Prior research conceptualized the mechanisms underlying HIV-related stigma and clinical outcomes, especially for the different types of HIV-related stigma (Earnshaw &

Chaudoir, 2009; Earnshaw et al., 2013; Turan et al., 2017). According to the Health Stigma Framework, HIV-related stigma can be categorized as internalized, anticipated, and enacted stigma (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013; Turan et al., 2017). Internalized stigma refers to internalized shame and is the recognition of stigma about oneself (Quinn & Earnshaw, 2011; Sayles, Wong, Kinsler, Martins, & Cunningham, 2009). Anticipated stigma is the belief of being discriminated among PLWH if others know their HIV status (Quinn & Earnshaw, 2011). Enacted stigma is the actual experience of being stigmatized among PLWH after their HIV status is known by others (Quinn & Earnshaw, 2011). The three types of HIV-related stigma impair clinical outcomes through affective and/or behavioral problems (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013; Turan et al., 2017).

Two well-investigated psycho-behavioral mechanisms of HIV-related stigma on clinical outcomes are psychological distress and ART adherence, and these mechanisms might be different across various levels of internalized, anticipated, and enacted stigma. For instance, the overall HIV-related stigma could negatively affect CD4 count through its impacts on depressive symptoms and ART adherence (Logie et al., 2019; Rao et al., 2012; Wang et al., 2009; Wood et al., 2004). In a test of Health Stigma Framework, Earnshaw and colleagues found that internalized, anticipated, and enacted stigma had different impacts on psychological, behavioral, and physical health outcomes (Earnshaw et al., 2013). Internalized stigma was closely associated with psychological wellbeing and treatment-related behaviors (e.g., medical visit, ART adherence) but not with comorbidities and CD4 count (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013). In contrast, anticipated and enacted stigma are the expectation and experiences of being stigmatized by others (Earnshaw & Chaudoir, 2009), and they were significantly related to treatment-related behaviors, comorbidities, and CD4 count but not to psychological wellbeing (Earnshaw et al., 2013). The findings suggested that the mediators between internalized, anticipated, enacted stigma and clinical outcomes might be different, and studies are needed to confirm these mechanisms. Additionally, most previous studies only investigated how HIV-related stigma influences clinical outcomes through the impacts on psychological distress. These studies might ignore the importance of psychological resources, especially for the treatment-related psychological resources (Turan et al., 2017).

Psychological resources, such as treatment-related self-efficacy, are important mechanisms through which HIV-related stigma may impact clinical outcomes (Turan et al., 2017). Psychological resources refer to the tools, skills, confidences, and motivations that PLWH use to cope with stressful events, keep daily routines, and maintain their health (Turan et al., 2017). HIV-related stigma may cause PLWH to believe that they are less capable and confident in dealing with treatment-related issues (i.e., medical visits, adherence behaviors), which may result in low self-efficacy related to ART adherence and suboptimal clinical outcomes (Seghatol-Eslami et al., 2017). For instance, using cross-sectional data, our research team found that the indirect effect from anticipated stigma to ART adherence through ART self-efficacy was significant (Zeng et al., 2020). However, limited studies have investigated the mechanisms of HIV-related stigma on clinical outcomes through psychological resources from a longitudinal perspective.

To address these knowledge gaps, the current study aims to examine the psycho-behavioral mechanisms of three types of HIV-related stigma (i.e., internalized, anticipated, enacted stigma) on clinical outcomes using data derived from a prospective cohort study in Guangxi, China. Guangxi, a resource-limited province located in the southern China, was ranked third across the 31 provinces in terms of the total number of HIV cases (Wu, Chen, Scott, & McGoogan, 2019). The HIV epidemic in Guangxi could be described as a rural phenomenon with large number of PLWH living in rural areas, from low socioeconomic status, and being infected mostly through sexual activity (Wang, 2013; Yang et al., 2019). Therefore, PLWH in Guangxi are at risk of HIV-related stigma and suboptimal clinical outcomes because of the traditional culture, limited HIV knowledge, and local HIV transmission patterns. Based on the Health Stigma Framework, we developed a conceptual model (Figure 4.8) and hypothesized that: (1) all three types of HIV-related stigma could influence clinical outcomes directly and indirectly; and (2) the psycho-behavioral mechanisms of stigma on clinical outcomes would be different by internalized, anticipated, and enacted stigma. Particularly, ART self-efficacy, HIV symptom management self-efficacy, and ART adherence were the psycho-behavioral mechanisms tested in this study.

5.3 Methods

Study setting and participants

Data derived from a prospective cohort study was used to accomplish the aims of this study. The original cohort was developed in Guangxi, China in November 2017. Using a systematic sampling approach, PLWH were recruited from six major public hospitals/clinics in five cities with largest number of HIV patients under care. PLWH who were aged between 18 and 60 years old, had a confirmed diagnosis of HIV, and had no plans to relocate outside of Guangxi in the next 12- month were considered as the eligible participants. Those who had mental/physical inabilities to finish the survey and/or who were currently incarcerated/institutionalized were excluded from the study.

Recruitment and data collection

The recruitment and data collection for this parent study have been described in detail elsewhere (Zeng et al., 2020). Briefly, once eligible PLWH were selected, local research assistants confirmed the patients for eligibility, scheduled a time to introduce the cohort study, and invited them to participate. After obtaining their written informed consent, research assistants had a one-on-one interview with patient in a private room of hospitals/clinics. Interviewers described the purpose of the assessment, assured participants of their confidentiality, and introduced the study aims and questionnaire. The interviewers provided assistance during the survey when needed. With an estimated 5% refusal rate, a total of 1,198 PLWH were recruited and finished the baseline assessment from November 2017 to February 2018. PLWH were followed up at 6-, 12-, 18-, 24-, 30-, and 36- months. Longitudinal data at baseline, 6-, 12-, and 18-month follow-ups were used in this study. Upon the completion of each assessment, all participants received a gift (e.g., household items) equivalent to US$ 5.00. The study protocol was approved by the Institutional Review Boards at both University of South Carolina in the United States and Guangxi CDC in China.

Measures

Clinical outcomes

Clinical outcomes included CD4 count, viral suppression, and HRQoL. Both CD4 count and viral load were retrieved from PLWH's electronic health records. Using 500 cells/µl as a cutoff (U.S. Department of Health and Human Services & Panel on

Antiretroviral Guidelines for Adults and Adolescents, 2017), CD4 count was categorized as a binary variable to evaluate the normal immunologic functioning. Viral suppression was defined as viral load less than or equal to 50 copies/ml in PLWH's plasma (Center for Disease Control and Prevention [CDC], 2018).

HRQoL was assessed using the 35- item Medical Outcomes Study HIV Health Survey (MOS-HIV) (Wu et al., 1997). It covered 11 dimensions of health quality including general health perception, physical functioning, role functioning, social functioning, cognitive functioning, pain, mental health, energy/fatigue, health distress, quality of life, and health transition. The score of each dimension was calculated and transformed to a score ranging from 0 to 100 (Delate & Coons, 2001; Hays & Shapiro, 1992; Ware & Sherbourne, 1992; Wu et al., 1997). The final score was the sum score of the 11- dimension and then transformed using the same method. A higher score of HRQoL indicated a higher level of HRQoL. The MOS-HIV scale showed good reliability among the participants in this study (Cronbach's alpha = 0.93).

Sociodemographic characteristics

Sociodemographic characteristics at baseline were used in this study. These characteristics included age, gender, marital status, ethnicity, types of residence, education attainment, employment, levels of monthly income, weight, and height. Weight and height were used to calculate body mass index (BMI), which was categorized as underweight (less than 18.5), normal/healthy weight (18.5 ~ 24.9), or overweight/obese (more than 24.9). HIV-related characteristics, such as time since HIV diagnosis, duration of ART, and transmission modes, were also included in the current study.

HIV-related stigma

Three common types of HIV-related stigma (i.e., internalized, anticipated, enacted stigma) were used in this study. Internalized stigma was measured using 8- item derived from the Berger HIV Stigma Scale (Berger, Ferrans, & Lashley, 2001), which captured "negative self-image" among PLWH. Anticipated stigma was assessed using 9- item derived from the Health Stigma Framework (Earnshaw et al., 2013). It evaluated the expectation of HIV-related stigma from family members, as well as in community and healthcare settings. Enacted stigma was evaluated using the 16-item checklist adapted from a previous study (Yi et al., 2015), which asked PLWH about their experiences of being stigmatized due to their HIV status in the last six months. The sum score of each type of HIV-related stigma was calculated, with a higher score indicating a higher level of stigma. All of these scales had good reliability at baseline (internalized stigma: Cronbach's alpha = 0.94; anticipated stigma: Cronbach's alpha=0.92; enacted stigma: Cronbach's alpha = 0.89). As most of the PLWH reported that they did not have any overt experiences of being stigmatized (n = 846 [71.3%] at baseline), enacted stigma was categorized as a binary variable to define stigmatized experiences (0 = no, 1 = yes) using zero as a cutoff.

Psycho-behavioral mediators

Psycho-behavioral mediators included in this study were ART self-efficacy, HIV symptom management self-efficacy, and ART adherence. ART self-efficacy was measured using the 10- item scale adapted from the Self-efficacy for Appropriate Medication Use Scale (SEAMS) (Risser, Jacobson, & Kripalani, 2007; Zhang et al., 2016). HIV symptom management self-efficacy was measured using six items from the

Self-efficacy for Managing Chronic Disease Scale (Eller et al., 2014) and four items about participants' confidence in symptom management (Lorig, Sobel, Ritter, Laurent, & Hobbs, 2001). The sum score of each self-efficacy was calculated according to relevant guidelines. A high score indicated a higher level of self-efficacy. Both of these two scales had good reliability at baseline (ART self-efficacy: Cronbach's alpha = 0.95; HIV symptom management self-efficacy: Cronbach's alpha = 0.96).

ART adherence was measured using five items adapted from the Adult AIDS Clinical Trials Group (AACTG) adherence instrument. Four items were used to ask PLWH about the days of completing their prescribed ART doses within four specified timeframes (last three days, last weekend, last two weeks, last month [30 days]). Percentage adherence of each timeframe was calculated based on a previous study (Da, Li, Qiao, Zhou, & Shen, 2018). Then, the percentage was categorized as a binary variable (0: $< 90.0\%$; 1: $\geq 90\%$) according to the Chinese guideline for ART treatment. The fifth item was used to ask PLWH whether they adhered to their prescribed doses (1 = always, 2 = very often, 3 = sometimes, 4 = rarely, 5 = never). Participants who always adhered to their prescription were coded as "yes (1)" while others were coded as "no (0)". The sum score of these five items was calculated. PLWH who scored five were considered as having optimal adherence to ART. The adherence measures showed acceptable reliability at baseline (Cronbach's alpha = 0.72).

Psychological confounders

Depression and anxiety at baseline were controlled for as potential psychological confounders in this study. Depression was assessed using the 10- item Center for Epidemiologic Studies-Depression (CES-D 10) Scale, which had been validated in

Chinese population (Yu, Lin, & Hsu, 2013). The Cronbach's alpha of this scale was 0.85 at baseline assessment. Anxiety was measured using the Brief Anxiety Scale (Zung, 1971), which also had been validated in Chinese culture (Zhang, Liu, Li, Mao, & Yuan, 2015). The original scale included 20 items, which asked PLWH about their feelings of anxiety disorder during last week. However, due to translation, two items ("My hands are usually dry and warm", "I fall asleep easily and get a good night's rest") could not reflect their original meanings, which resulted in Cronbach's alpha of 0.80 in the overall scale. According to the exploratory factor analysis, the reliability was significantly improved after deleting these two items (Cronbach's alpha = 0.88). The sum score of each scale was generated. PLWH with higher scores in these two scales had higher levels of psychological distress.

Statistical analysis

Statistical analysis included descriptive statistics, latent growth curve modelling (LGCM), bivariate analysis, and mediation analysis. First, sociodemographic characteristics were described using *mean* (*standard deviation* [*SD*]) for continuous variables and *frequency* (*percentage* [%]) for categorical variables.

Second, measurement models of all key variables in conceptual model were constructed using unconditional LGCM. As this study focused on examining the longitudinal mediating effects of psycho-behavioral mediators, the changes of all variables of interest were defined as linear trend (time scores: 0, 1, 2, 3). What is more, using linear trend to define change patterns could reduce the risk of model misidentification. LGCM with continuous outcomes were used for internalized stigma, anticipated stigma, ART self-efficacy, HIV symptom management self-efficacy, and

HRQoL while LGCM with binary outcomes were used for enacted stigma, ART adherence, CD4 count, and viral suppression. In the process of LGCM with binary outcomes, logit link function was specified. Multiple indices, such as χ^2, χ^2/*degree of freedom* (*df*), *p*-value, *Comparative Fit Index* (*CFI*), *Tucker-Lewis Index* (*TLI*), *Root Mean Square Error of Approximation* (*RMSEA*), and *Standardized Root Mean Residual* (*SRMR*), were used to evaluate the model fit of each measurement model. For continuous variables, smaller χ^2 value, $\chi^2/df \leq 3.00$, $p > 0.05$, $CFI > 0.95$, $TLI > 0.95$, $RMSEA \leq 0.06$, and $SRMR \leq 0.08$ indicated better model fit (Hu & Bentler, 1999; Muthen & Muthen, 2018). In terms of binary variables, smaller χ^2 value, $\chi^2/df \leq 3.00$, $p > 0.05$ indicated better model fit (Muthen & Muthen, 2018; Schermelleh-Engel, Moosbrugger, & Müller, 2003). *Mean* and *standard error* (*SE*) were used to describe intercept and slope while *r* was used to describe the correlation between them. Since all continuous variables were not in normal distribution, using their original values to construct measurement models could not obtain good model fits and capture the information of all participants. With the consideration of interpretation, standardized transformation was employed to re-estimate the intercepts and slopes of all continuous variables before mediation analysis.

Third, the estimated intercepts and slopes of all key variables in conceptual model were output for bivariate analysis. Spearman correlation analysis was used to examine the correlations among intercepts or slopes of all key variables. Bivariate analyses of the slopes of clinical outcomes (i.e., CD4 count, viral suppression, HRQoL) and sociodemographic characteristics and psychological confounders were conducted. Spearman correlation analysis was used for examining the correlations between continuous variables while Wilcoxon rank-sum test or Kruskal-Wallis test were used for the relationships between slopes and categorical variables.

Finally, intercepts and slopes of all key variables were used for mediation analysis after adjusting for covariates with *p*-values less than 0.05 in bivariate analyses. First of all, intercept and slope were specified as correlating with each other for each key variable, and path model was constructed based on the conceptual model. Moreover, to improve model fit, based on the model trimming strategy (Ullman, 2001), paths with non-significant *p*-values were deleted. Furthermore, path model was modified to improve the model fit based on the modification indices and theoretical knowledge (Ullman, 2001; J. Wang & Wang, 2019). Path coefficient and its 95% confidence interval (*CI*), standardized coefficient, and *p*-value were reported. Finally, longitudinal mediating effects from the slopes of HIV-related stigma to those of clinical outcomes through the slopes of psycho-behavioral mediators were tested using bias-corrected bootstrap procedure based 1,000 bootstrap samples (Wang & Wang, 2019). Bias-corrected 95%*CI* of the indirect paths were reported (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Delta *z* score was used as a statistics to evaluate indirect effects (Muthen & Muthen, 2018). Robust maximum likelihood estimation (estimator = MLR) was used to estimate the parameters, and full information maximum likelihood (FIML) estimation approach was used to handle missing data. Same indices, such as χ^2, χ^2/df, *p*-values, *CFI*, *TLI*, *RMSEA*, and *SRMR*, were used to assess the model fit.

Bivariate analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). LGCM and mediation analysis were performed using Mplus version 7.0 (Muthen & Muthen, Los Angeles, CA).

5.4 Results

Descriptive statistics

Among the 1,198 PLWH, the average age and time since HIV diagnosis were 39.0 (*SD* = 9.2) and 5.5 (*SD* = 3.1), respectively. More than 60.0% of them were male (771 [64.4%]) and/or infected through sexual activity (832 [69.7%]). There were 72.9% (873/1,198) of the participants in normal/healthy weight. Table 5.1 shows detailed information of sociodemographic characteristics among participants at baseline.

Table 5.2 shows descriptive statistics of key factors in conceptual model across the four-wave datasets. The average attrition rate of these four-wave datasets was less than 5.0%. Nearly 45.0% of participants had CD4 counts equal to or higher than 500 cells/μl, and 95.0% of participants had achieved viral suppression. The average score of HRQoL across the four-wave follow-up was higher than 70.0 out of 100.0.

The percentages of PLWH who had experiences of being stigmatized for each assessment were 28.7% (341/1,187), 21.6% (258/1,195), 16.6% (193/1,159), and 22.4% (260/1,158), respectively. More than 80.0% of the PLWH at each assessment had optimal self-report ART adherence.

Measurement models

Results of unconditional LGCM revealed that the measurement models of categorical outcomes (i.e., enacted stigma, ART adherence, CD4 count, viral suppression) were good except that of CD4 count. The mean values of these variables reflected the log probabilities of having stigmatized experiences, optimal adherence, normal CD4 count, and viral suppression among PLWH at baseline assessment. Only the slopes of enacted stigma and CD4 count were statistically significant, which suggested that there were significant changes in the probabilities of stigmatized experiences (slope = -0.224, $p < 0.01$) and normal CD4 count (slope = 0.140, $p < 0.05$) across the time.

In terms of the continuous variables (i.e., internalized stigma, anticipated stigma, ART self-efficacy, HIV symptom management self-efficacy, HRQoL), the measurement models had adequate model fits except that of internalized stigma (χ^2/df =14.846, *RMSEA*=0.108, *CFI* = 0.876, *TLI* = 0.851, *SRMR* = 0.059). The intercepts of these continuous variables reflected their initial levels among PLWH at baseline. Only the slopes of internalized stigma (slope = -0.237, $p < 0.001$), anticipated stigma (slope = -0.476, $p < 0.001$), and HIV symptoms management self-efficacy (slope = -0.324, $p < 0.001$) were statistically significant, which meant that these factors had significant changes over time. The unsatisfied model fits in continuous variables suggested that transformation was needed before the mediation analysis. After standardization, all of the measurement models had good model fits. Table 5.3 shows the model fits of measurement models before and after standardization, and Table 5.4 shows the parameter estimation of each measurement model.

Bivariate analysis

Table 5.5 shows the correlation matrices of intercepts and slopes among variables of interest. The correlation matrix of intercepts found that the intercept of internalized stigma was significantly and negatively associated with that of HRQoL (r = -0.48) but not with those of CD4 count (r = 0.01) and viral suppression (r = -0.01). Similar findings could be found in the relationships between the intercepts of anticipated stigma, CD4 count, viral suppression, and HRQoL. The intercept of enacted stigma was significantly and negatively related to those of CD4 count (*r* = -0.07), viral suppression (*r* = -0.06), and HRQoL (*r* = -0.31).

Correlation matrix of slopes found that all slopes of internalized (*r* = -0.33), anticipated (*r* = -0.25), and enacted stigma (*r* = -0.22) were significantly and negatively associated with that of HRQoL, but only the slope of internalized stigma was significantly correlated with that of CD4 count (*r* = 0.08). No significant relationships were found between the slopes of all three HIV-related stigma and that of viral suppression. Unexpectedly, the slope of HIV symptom management self-efficacy was negatively related to the slope of CD4 count ($r = -0.07$, $p < 0.05$).

Tables 5.6, 5.7, and 5.8 show the bivariate analyses of the slopes of CD4 count, viral suppression, and HRQoL, respectively. Significant relationships were found in the slope of CD4 count and age, time since HIV diagnosis, duration of ART, gender, ethnicity, types of residence, education attainment, transmission modes, depression, and anxiety at baseline. The slope of viral suppression was significantly associated with baseline time since HIV diagnosis, duration of ART, and depression. In terms of HRQoL, only marital status, transmission modes, depression, and anxiety were significantly associated with the slope of HRQoL.

Path model and mediation analysis

CD4 count

After adjusting for covariates with *p*-values less than 0.05 in bivariate analysis, path model with CD4 count as a primary outcome was constructed based on the conceptual model. Model fit indices revealed that the original model did not have a good model fit ($\chi^2/df = 11.282$, $p < 0.001$, *RMSEA* = 0.093, *CFI* = 0.665, *TLI* = 0.654, *SRMR* =

0.090). Using model trimming strategy, insignificant paths were deleted (Appendix C). The model fit did not have significant change (χ^2/df = 15.218, p < 0.001, *RMSEA* = 0.109, *CFI* = 0.678, *TLI* = 0.657, *SRMR* = 0.108). Based on the modification indices (Appendix D) and theoretical knowledge, correlations among the intercepts of key variables were added to the existing model, and the model fit had significant improvement (χ^2/df = 5.506, p < 0.001, *RMSEA* = 0.061, *CFI* = 0.922, *TLI* = 0.891, *SRMR* = 0.062) (Table 5.9).

Table 5.10 shows the coefficients of final model with CD4 count as an outcome. The slope of ART adherence was negatively associated with the slope of CD4 count (β = -0.058, p = 0.034). The positive change of ART adherence led to negative change in CD4 count. The slopes of all three types of HIV-related stigma were negatively associated with that of ART self-efficacy (internalized stigma: β = -0.114, p < 0.001; anticipated stigma: β = -0.123, p < 0.001; enacted stigma: β = -0.197, p < 0.001). These implied that the increases of internalized, anticipated, and enacted stigma led to the decrease of ART self-efficacy. The slope of HIV symptom management self-efficacy was significantly related to the slope of anticipated stigma (β = -0.062, p < 0.001) but not to that of internalized stigma (β = -0.012, p = 0.199). This path implied that only the increase of anticipated stigma could result in the decrease of HIV symptom management self-efficacy. The slope of ART adherence was negatively associated with that of enacted stigma (β = -0.057, p = 0.005) and positively related to the slopes of ART self-efficacy (β = 0.066, p < 0.001) and HIV symptom management self-efficacy (β = 0.079, p = 0.045).

Result of mediation analysis found that none of the indirect paths from the slopes of HIV-related stigma to that of CD4 count were statistically significant. However, significant indirect effects from the slopes of HIV-related stigma to the slope of ART adherence were found in the final model. The increases of internalized (β = -0.007, delta z = -3.031, p = 0.002), anticipated (β = -0.008, delta z = -3.371, p = 0.001), and enacted stigma (β = -0.013, delta z = -3.312, p = 0.001) resulted in the decreases of ART adherence through reducing the changes of ART self-efficacy. Table 5.11 shows detailed results of mediation analysis of CD4 count.

Viral suppression

A path model with viral suppression as an outcome was constructed based on the conceptual model after adjusting for the significant covariates in bivariate analysis. The original model did not have a good model fit (χ^2/df = 18.841, p < 0.001, *RMSEA* = 0.122, *CFI* = 0.763, *TLI* = 0.711, *SRMR* = 0.111) (Table 5.9). Insignificant paths were deleted based on the model trimming strategy (Appendix C). However, the model fit did not have significant improvement (χ^2/df = 17.393, p < 0.001, *RMSEA* = 0.117, *CFI* = 0.763, *TLI* = 0.734, *SRMR* = 0.111). The final model had good model fit (χ^2/df = 5.248, p < 0.001, *RMSEA* = 0.060, *CFI* = 0.946, *TLI* = 0.924, *SRMR* = 0.059) after adding the correlations among the intercepts of key variables based on the modification indices and theoretical knowledge.

Table 5.12 shows the coefficients of the final model. The change of ART adherence could negatively influence the change of viral suppression (β = -0.035, p = 0.003). The slopes of internalized (β = -0.112, p < 0.001), anticipated (β = -0.123, p < 0.001), and enacted stigma (β = -0.196, p < 0.001) was negatively associated with that of ART self-efficacy. The change of HIV symptom management self-efficacy was significantly related to the change of anticipated stigma (β = -0.061, p < 0.001) but not to that of internalized stigma (β = -0.012, p = 0.210). The slope of ART adherence was negatively associated with that of enacted stigma (β = -0.056, p = 0.005) and positively related to the slopes of ART self-efficacy (β = 0.066, $p < 0.001$) and HIV symptom management self-efficacy (β = 0.080, p = 0.045).

Results of mediation analysis found that the series mediating effect from the slopes of HIV-related stigma, ART self-efficacy, ART adherence to that of viral suppression were statistically significant (internalized stigma: β = 0.000, delta z = 2.125, p = 0.034; anticipated stigma: β = 0.000, delta z = 2.269, p = 0.023; enacted stigma: β = 0.000, delta z = 2.118, p = 0.034). The increases of HIV-related stigma resulted in the decrease of ART self-efficacy, which in turn led to the decrease of ART adherence. The decrease of ART adherence resulted in the increase of viral suppression. However, the effect sizes of these indirect paths were close to zero. The changes of internalized (β = -0.007, delta z = -3.009, p = 0.003), anticipated (β = -0.008, delta z = -3.364, p = 0.001), enacted stigma (β = -0.013, delta z = -3.308, p = 0.001) could reduce the change of ART adherence through their negative impacts on the change of ART self-efficacy. Table 5.13 shows the results of mediation analysis of viral suppression.

Health-related quality of life (HRQoL)

A similar modelling procedure was used to construct the path model of HRQoL. The final model showed an adequate model fit (χ^2/df = 6.760, $p < 0.001$, *RMSEA* = 0.069, *CFI* = 0.926, *TLI* = 0.876, *SRMR* = 0.065) (Table 5.9).

Table 5.14 shows the coefficients of the final model with HRQoL as an outcome. Both the changes of internalized (β = -0.184, $p < 0.001$) and enacted stigma (β = -0.302, $p < 0.001$) negatively influence the change of HRQoL while the changes of ART self-efficacy (β = 0.386, $p < 0.001$) and HIV symptom management self-efficacy (β = 0.999, p

< 0.001) showed positive effects. The increases of three types of HIV-related stigma resulted in the decrease of ART self-efficacy but only the increase of anticipated stigma led to the decrease of HIV symptoms management self-efficacy (β = -0.062, p < 0.001). The change of ART adherence was negatively associated with the change of enacted stigma (β = -0.053, p = 0.003) but positively related to that of ART self-efficacy (β = 0.065, p < 0.001) and HIV symptom management self-efficacy (β = -0.087, p = 0.019).

Results of mediation analysis revealed that all three types of HIV-related stigma could affect the change of HRQoL through the impacts on the change of ART self-efficacy (internalized stigma: β = -0.049, delta z = -3.766, p < 0.001; anticipated stigma: β = -0.047, delta z = -3.903, p < 0.001; enacted stigma: β = -0.082, delta z = -4.265, p < 0.001). The increases of HIV-related stigma led to the decrease of ART self-efficacy, which in turn resulted in the decrease of HRQoL. Only anticipated stigma could lead to the negative change of HRQoL through the negative impact on HIV symptom management self-efficacy (β = -0.062, delta z = -4.960, p < 0.001). Similarly, internalized (β = -0.008, delta z = -3.202, p = 0.001), anticipated (β = -0.008, delta z = -3.309, p = 0.001), and enacted stigma (β = -0.014, delta z = -3.396, p = 0.001) led to the negative change of ART adherence through their negative impacts on ART self-efficacy. However, only anticipated stigma affected the change of ART adherence through its negative impact on the change of HIV symptom management self-efficacy (β = -0.005, delta z = -2.055, p = 0.040). The results of mediation analysis of HRQoL are shown in Table 5.15.

5.5 Discussion

Using data derived from a prospective cohort study and longitudinal mediation analysis, the current study investigated the mechanisms of different types of HIV-related stigma (i.e., internalized, anticipated, and enacted stigma) on clinical outcomes (i.e., CD4 count, viral suppression, and HRQoL) through psycho-behavioral paths. Results of longitudinal mediation analyses found that internalized, anticipated, and enacted stigma had different direct impacts on the three clinical outcomes, and their mechanisms on clinical outcomes were also different. Psychological resources could mediate the relationship between HIV-related stigma and health outcomes. To our knowledge, this is the first study exploring the differential psycho-behavioral mechanisms of HIV-related stigma on clinical outcomes based on the Health Stigma Framework. The findings from this study have important implications for stigma research and practical intervention.

Internalized, anticipated, and enacted stigma may affect HRQoL through their impacts on psychological resources. All three types of HIV-related stigma could decrease ART self-efficacy, which in turn affects HRQoL. This finding was consistent with that of the previous study (Zeng et al., 2020). Additionally, our study leveraged cohort data and longitudinal mediation analysis to test the impacts of HIV-related stigma on ART self-efficacy and how these impacts influenced HRQoL sequentially. PLWH with high levels of internalized and anticipated stigma might be more likely to have negative cognitions and beliefs about themselves (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013; Quinn & Earnshaw, 2011). What is more, PLWH who had stigmatized experiences might have low levels of motivation to engage in and maintain their HIV care and to utilize healthcare resources (Quinn & Earnshaw, 2011). These negative beliefs and low motivation are closely related to the confidence in ART adherence and medical visit, which in turn might affect the physical wellbeing of PLWH. This study also found that only anticipated stigma impaired HRQoL through reducing HIV symptom management self-efficacy. Compared with internalized and enacted stigma, anticipated stigma captures the fears of being mistreated in family, community, and healthcare settings, which may have strong association with the confidence in managing HIV-related symptoms, maintaining daily routine, and controlling disease progression (Eller et al., 2014; Lorig et al., 2001; Quinn & Earnshaw, 2011). The low confidence in these aspects could affect the multiple dimensions of HRQoL, such as pain, social functioning, cognitive functioning, physical health, and mental health (Wu et al., 1997).

Psychological resources and ART adherence could mediate the relationship between HIV-related stigma and viral suppression, but such mediating effects were not found in the indirect pathways from stigma to CD4 count. Unexpectedly, the serial mediating effects from HIV-related stigma, ART self-efficacy, ART adherence to viral suppression were significant and positive even though the effect sizes were small. This might be due to the negative association between changes of ART adherence and viral suppression in path model. The Health Belief Model and perception of disease severity could be used to explain this finding (Gao, Nau, Rosenbluth, Scott, & Woodward, 2000; Spire et al., 2002). PLWH with better health and lower perception of disease severity might be less like to adhere to ART (Gao et al., 2000). For instance, Gao and colleagues (2000) found that asymptomatic PLWH had lower perception of disease severity, which in turn resulted in suboptimal adherence as compared to those with symptoms. In our study, more than 90.0% of the participants achieved viral suppression but only 63.9% of the PLWH had consistently optimal adherence across the four-wave dataset. Additionally, it often only takes no longer than three months to achieve viral suppression after ART initiation. The low perception of risk and short duration to suppress viral load may make PLWH perceive that it may not cause serious consequences if they occasionally miss some of the prescribed doses, especially in the situations of suffering from discrimination or stigma. We also conducted a multiple group mediation analysis based on the baseline CD4 count (0: < 500 cells/μl; 1: ≥ 500 cells/μl), and the results confirmed our explanation. The negative relationship between slopes of ART adherence and viral suppression was only found in PLWH with CD4 count equal to or higher than 500 cells/μl, and the serial mediating effects from HIV-related stigma, ART self-efficacy, ART adherence to viral suppression were not significant in both two groups (Appendix E). However, psychological resources and ART adherence did not show a mediating effect between HIV-related stigma and CD4 count. The possible explanation for these findings was that the change of CD4 count is usually affected by multiple factors, such as the CD4 count before ART initiation, age, and duration of ART (i-base, 2016, 2019). Additionally, it often takes a long time to see changes in CD4 count (i-base, 2016, 2019). Future studies with long-term follow-up and considering more confounders are needed to confirm this finding.

HIV-related stigma could deter ART adherence through reducing ART self-efficacy. This finding was consistent with that of a previous study (Zeng et al., 2020). PLWH with negative cognitions about themselves, beliefs about being discriminated in family, community and healthcare settings, and/or stigmatized experiences might have few confidence and motivation to adhere to ART regimens, which might lead to suboptimal adherence behaviors (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013; Quinn & Earnshaw, 2011; Zeng et al., 2020). In terms of the inconsistent mediating effect of HIV symptom management self-efficacy between anticipated stigma and ART adherence across the three models, this might be due to the weak correlation between the change of anticipated stigma and that of HIV symptom management self-efficacy. Even though both changes of anticipated stigma and HIV symptom management self-efficacy were significant in the unstandardized measurement models, the changes were small which may result in limited influence on each other.

The findings from this study had some important implications for stigma research and intervention. From the research perspective, the differential psycho-behavioral mechanisms of HIV-related stigma on the three clinical outcomes implies that future stigma research should consider the characteristics of each type of HIV-related stigma and clinical outcome and use these knowledge to frame the pathways between them. Additionally, psychological resources, such as ART self-efficacy, could mediate the relationship between HIV-related stigma and ART adherence and clinical outcomes. This finding confirmed that psychological resources are important mechanisms of stigma and health outcomes and future research are needed to explore their role, in addition to the psychological distress, such as depression and anxiety (Turan et al., 2017). In terms of the practical implication, to reduce the negative impacts of HIV-related stigma on health outcomes, multilevel interventions tailored to different types of stigma are needed. As internalized and anticipated stigma refer to the negative cognition process and beliefs at the intrapersonal level, which could make PLWH believe that the negative attributes related to HIV are true of the self, feel fear of being stigmatized, and avoid retaining in care (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013), psychological counseling and resilience-based interventions, such as coping strategies, emotional regulation, and stress management, could alleviate their negative influences (Rao et al., 2019). In contrast, enacted stigma involves the stigmatized experiences from others or in the public. Therefore, structural intervention, such as public health education, could potentially correct misinformation and misunderstandings about HIV and reduce discrimination against PLWH (Rao et al., 2019). What is more, the significant mediating effect of treatment-related self-efficacy suggested that interventions promoting confidence and motivation to health behaviors, such as skills training, self-management, and problem-solving, are also very effective in buffering the negative influences of HIV-related stigma, maintaining treatment-related behaviors, and improving clinical outcomes (Areri, Marshall, & Harvey, 2020).

Although this study is innovative in examining the longitudinal mechanisms of HIV-related stigma on clinical outcomes, some limitations need to be acknowledged. First, self-report measures were employed to assess variables of interest, which might result in self-report bias. For instance, the ART adherence in this study might be overestimated because of social desirability bias even though we used a multiple item approach to assess the variable (Stirratt et al., 2015). To assess ART adherence adequately, objective measurement tools, such as biomarkers and device-based measurement, are needed. Additionally, due to social desirability bias, the percentage of PLWH with stigmatized experiences might be underestimated. There were more than 70% of the PLWH without stigmatized experiences in the last 6 months. Future research is needed to improve the validity of the measure of enacted stigma. Second, ART self-efficacy, HIV symptom management self-efficacy, and ART adherence were the major psycho-behavioral mechanisms examined in this study. However, other psycho-behavioral factors, such as resilience and positive coping, may also mediate the relationship between stigma and clinical outcomes (Turan et al., 2017). Future studies are needed to investigate their mediating roles.

Third, the measurement model of CD4 count did not have a good model fit, which might threaten the internal validity of the findings in this study. However, we also constructed the measurement model of CD4 count with free estimation, but its model fit was worse than the current model ($\chi^2/df = 9.77$, $p < 0.001$). The possible reason for the unsatisfied model fit may be that we constructed the measurement model using the binary variable of CD4 count which only provided limited information for modelling. Future studies with CD4 count as a continuous variable are needed to confirm our finding. Fourth, only four waves of data across the two-year project were used in this study, which might limit the ability for capturing significant changes among variables of interest. Fifth, PLWH in this study were recruited from the hospitals/clinics. Therefore, they might have better clinical outcomes, lower HIV-related stigma, and higher treatment-related self-efficacy as compared to those who were not engaged in care in hospitals/clinics. These characteristics might restrict our ability to test the conceptual model. Future studies with diverse PLWH are needed to test the conceptual model of the current study. Sixth, survey approach was employed to investigate the research hypotheses in this study. However, to obtain a comprehensive picture of the cultural context, qualitative studies could be used in future to collect more detailed information in order to explain the complex mechanisms of HIV-related stigma on clinical outcomes.

Finally, as this study was conducted in Guangxi, China, cautions are needed when generalizing the findings from this study to other areas of China or other cultural settings.

5.6 Conclusion

Findings from this study support that HIV-related stigma affects important clinical outcomes through differential psycho-behavioral mechanisms. Future stigma studies should consider the characteristics of each type of stigma and clinical outcomes when framing the pathways between them. Psychological resources are important mechanisms between stigma and health outcomes and should be incorporated into future stigma research. To improve clinical outcomes among PLWH effectively, future intervention studies should also target psychological resources, improve resilience, and maintain optimal adherence behaviors besides the three types of HIV-related stigma at both intrapersonal and interpersonal levels.

5.7 References

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Table 5.1 Sociodemographic characteristics of PLWH at baseline assessment (*n*=1,198)

Variables	**N (%)**	**Variables**	**N (%)**
Age in years (*Mean*, *SD*)	39.0 (±9.2)	Depression (*Mean*, *SD*)	6.6 (±4.7)
Time since HIV diagnosis in year (*Mean*, *SD*)	5.5 (±3.1)	Anxiety (*Mean*, *SD*)	26.9 (±6.4)
Duration of ART in years (*Mean*, *SD*)	4.8 (±3.0)	Education attainment	
Gender		Less than or equal to middle school	719 (60.0)
Male	771 (64.4)	High school or above	479 (40.0)
Female	427 (35.6)	Employment	
Marital status		Unemployed	220 (18.5)
Single/ separated	360 (30.4)	Part time	235 (19.8)
Married/ cohabitated	666 (56.2)	Full time	734 (61.7)
Divorced/ widowed	160 (13.4)	Levels of monthly income	
Ethnicity		No more than 1,999 RMB	370 (31.0)
Han	778 (65.0)	2,000 ~ 3,999 RMB	584 (48.9)
Non-Han	419 (35.0)	At least 4,000 RMB	241 (20.2)
Types of residence		Body Mass Index	
City	536 (44.9)	Underweight	161 (13.4)
County	231 (19.3)	Normal/healthy weight	873 (72.9)
Rural	428 (35.8)	Overweight/obese	164 (13.7)
Transmission modes			
Sexual activity	832 (69.7)		
Others	361 (30.3)		

Note: *SD*: Standard deviation.

Table 5.2 Descriptive statistics of key variables across the four-wave datasets

Variables	**Baseline**	**6-month**	**12-month**	**18-month**
Sample sizes (*n*, %)	1,198 (100.0)	1,197 (99.9)	1,163 (97.1)	1,161 (96.9)
Attrition rates (*n*, %)	-	1 (0.1)	35 (2.9)	37 (3.1)
Clinical outcomes				
CD4 count (*n*, %)				
Less than 500 cells/µl	658 (54.9)	657 (54.8)	656 (54.8)	635 (53.0)
500 cells/µl or more	540 (45.1)	541 (45.2)	542 (45.2)	563 (47.0)
Viral suppression (*n*, %)				
Yes	1,130 (94.3)	1,145 (95.8)	1,109 (95.4)	1,135 (97.8)
No	68 (5.7)	50 (4.2)	54 (4.6)	26 (2.2)
Health-related quality of life (*Mean*, *SD*)	73.7 (±13.1)	71.2 (±13.4)	74.0 (±12.4)	72.1 (±13.3)
Predictors				
Internalized stigma (*Mean*, *SD*)	16.3 (±5.5)	17.0 (±5.0)	15.5 (±4.7)	16.0 (±5.1)
Anticipated stigma (*Mean*, *SD*)	23.2 (±7.7)	22.6 (±7.2)	21.2 (±6.8)	22.0 (±7.1)
Enacted stigma (*Mean*, *SD*)				
Yes	341 (28.7)	258 (21.6)	193 (16.6)	260 (22.4)
No	846 (71.3)	937 (78.4)	966 (83.4)	898 (77.6)
ART self-efficacy (*Mean*, *SD*)	24.5 (±5.0)	23.7 (±5.0)	24.5 (±5.0)	24.2 (±5.3)
HIV symptom management self-efficacy (*Mean*, *SD*)	33.5 (±9.1)	34.1 (±7.5)	34.2 (±7.6)	32.6 (±8.5)
ART adherence (*n*, %)				
Optimal	963 (80.8)	981 (82.2)	983 (85.5)	928 (80.1)
Suboptimal	229 (19.2)	213 (17.8)	167 (14.5)	230 (19.9)

Note: *SD*: Standard deviation.

Table 5.3 Measurement models of key variables

Variables	χ^2	χ^2/df	***p*-values**	***RMSEA***	***CFI***	***TLI***	***SRMR***
Unstandardized							
Internalized stigma	74.223	14.846	<0.001	0.108	0.876	0.851	0.059
Anticipated stigma	39.330	7.866	<0.001	0.076	0.930	0.917	0.034
Enacted stigma	32.314	3.231	<0.001	-	-	-	-
ART self-efficacy	39.850	7.970	<0.001	0.076	0.942	0.931	0.048
HIV symptom management self-efficacy	58.320	11.664	<0.001	0.094	0.926	0.912	0.081
ART adherence	38.166	3.817	<0.001	-	-	-	-
CD4 count	86.861	8.686	<0.001	-	-	-	-
Viral suppression	32.038	3.204	<0.001	-	-	-	-
Health-related quality of life	77.526	15.505	<0.001	0.110	0.900	0.880	0.074
Standardized							
Internalized stigma	0.880	0.176	0.972	0.000	1.000	1.009	0.007
Anticipated stigma	4.503	0.901	0.480	0.000	1.000	1.001	0.011
ART self-efficacy	8.584	1.717	0.127	0.024	0.994	0.993	0.019
HIV symptom management self-efficacy	17.241	3.448	0.004	0.045	0.983	0.980	0.031
Health-related quality of life	16.649	3.330	0.005	0.044	0.984	0.981	0.032

Table 5.4 Parameter estimation of measurement models

Variables	***Intercept***		***Slope***		***Correlation between Intercept and slope***
	Mean	*SE*	*Mean*	*SE*	
Unstandardized					
Internalized stigma	**16.538*****	0.148	**-0.237*****	0.061	**-0.579*****
Anticipated stigma	**22.955*****	0.200	**-0.476*****	0.082	**-0.428*****
Enacted stigma	**-1.498*****	0.122	**-0.224*****	0.069	**-0.578*****
ART self-efficacy	**24.222*****	0.139	0.007	0.059	**-0.408*****
HIV symptom management self-efficacy	**32.209*****	0.223	**-0.324*****	0.088	0.018
ART adherence	**2.478*****	0.186	-0.138	0.088	**-0.757*****
CD4 count	**-0.887*****	0.214	**0.140***	0.065	**-0.641*****
Viral suppression	**7.676*****	0.738	-0.456	0.337	**-0.796*****
Health-related quality of life	**73.091*****	0.374	-0.191	0.145	**-0.364*****
Standardized					
Internalized stigma	-0.002	0.145	0.000	0.060	**-0.580*****
Anticipated stigma	0.000	0.199	-0.007	0.083	**-0.428*****
ART self-efficacy	0.004	0.135	0.000	0.058	**-0.414*****
HIV symptom management self-efficacy	0.025	0.222	-0.015	0.086	-0.054
Health-related quality of life	0.020	0.363	-0.034	0.141	**-0.368*****

Note: *SE*: Standard error; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 5.5 Correlation matrix of intercepts and slopes among variables of interest

Variables	1.	2.	3.	4.	5.	6.	7.	8.	9.
Intercepts									
1. Internalized stigma	1.00								
2. Anticipated stigma	**0.47*****	1.00							
3. Enacted stigma	**0.25*****	**0.24*****	1.00						
4. ART self-efficacy	**-0.37*****	**-0.29*****	**-0.15*****	1.00					
5. HIV symptom management self-efficacy	**-0.42*****	**-0.40*****	**-0.23*****	**0.57*****	1.00				
6. ART adherence	-0.01	-0.003	**-0.06***	**0.16*****	**0.08****	1.00			
7. CD4 count	0.01	0.03	**-0.07***	**0.09****	**0.16*****	-0.01	1.00		
8. Viral suppression	-0.01	0.02	**-0.06***	**0.07***	0.03	**0.09****	0.06	1.00	
9. Health-related quality of life	**-0.48*****	**-0.35*****	**-0.31*****	**0.51*****	**0.55*****	**0.10*****	0.05	0.06	1.00
Slopes									
1. Internalized stigma	1.00								
2. Anticipated stigma	**0.36*****	1.00							
3. Enacted stigma	**0.17*****	**0.13*****	1.00						
4. ART self-efficacy	**-0.21*****	**-0.20*****	**-0.15*****	1.00					
5. HIV symptom management self-efficacy	**-0.13*****	**-0.24*****	-0.03	**0.21*****	1.00				
6. ART adherence	-0.04	-0.05	**-0.09****	**0.16*****	**0.09****	1.00			
7. CD4 count	**0.08****	0.04	0.04	-0.02	**-0.07***	-0.05	1.00		
8. Viral suppression	-0.03	-0.03	0.06	0.03	-0.03	-0.03	0.01	1.00	
9. Health-related quality of life	**-0.33*****	**-0.25*****	**-0.22*****	**0.35*****	**0.24*****	**0.09****	-0.02	0.01	1.00

Note: *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 5.6 Bivariate analysis of the change (slope) in CD4 count

Variables	**Slope of CD4 count** ***r* or mean (*SD*)**	***p*-value**
Age in years	0.09	**0.001****
Time since HIV diagnosis in years	-0.14	**<0.001*****
Duration of ART in years	-0.11	**<0.001*****
Gender		**0.001****
Male	0.18 (0.54)	
Female	0.07 (0.59)	
Marital status		0.956
Single/separated	0.14 (0.56)	
Married/cohabitated	0.14 (0.56)	
Divorced/widowed	0.14 (0.59)	
Ethnicity		**0.007****
Han	0.17 (0.56)	
Non-Han	0.08 (0.56)	
Types of residence		**<0.001*****
City	0.09 (0.56)	
County	0.07 (0.61)	
Rural	0.25 (0.52)	
Education attainment		**<0.001*****
Less than or equal to middle school	0.19 (0.56)	
High school or above	0.07 (0.56)	
Employment		0.263
Unemployed	0.13 (0.55)	
Part time	0.08 (0.59)	
Full time	0.16 (0.56)	
Levels of monthly income		0.155
No more than 1,999 RMB	0.14 (0.56)	
2,000 ~ 3,999 RMB	0.17 (0.56)	
At least 4,000 RMB	0.08 (0.57)	
Transmission modes		**<0.001*****
Sexual activity	0.17 (0.57)	
Others	0.07 (0.57)	
Body Mass Index		0.593
Underweight	0.17 (0.56)	
Normal/healthy weight	0.14 (0.56)	
Overweight/obese	0.10 (0.58)	
Depression	-0.06	**0.032***
Anxiety	-0.07	**0.013***

Note: *SD*: Standard deviation; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. All variables were selected at baseline assessment.

Table 5.7 Bivariate analysis of the change (slope) in viral suppression

Variables	**Slope of viral suppression** ***r* or mean (*SD*)**	***p*-value**
Age in years	0.01	0.835
Time since HIV diagnosis in years	-0.09	**0.002****
Duration of ART in years	-0.09	**0.002****
Gender		0.536
Male	-0.45 (0.43)	
Female	-0.47 (0.36)	
Marital status		0.798
Single/separated	-0.44 (0.43)	
Married/cohabitated	-0.46 (0.41)	
Divorced/widowed	-0.49 (0.33)	
Ethnicity		0.267
Han	-0.46 (0.40)	
Non-Han	-0.45 (0.41)	
Types of residence		0.098
City	-0.48 (0.37)	
County	-0.48 (0.35)	
Rural	-0.42 (0.47)	
Education attainment		0.536
Less than or equal to middle school	-0.45 (0.42)	
High school or above	-0.47 (0.38)	
Employment		0.767
Unemployed	-0.46 (0.40)	
Part time	-0.48 (0.35)	
Full time	-0.45 (0.42)	
Levels of monthly income		0.846
No more than 1,999 RMB	-0.47 (0.36)	
2,000 ~ 3,999 RMB	-0.45 (0.42)	
At least 4,000 RMB	-0.45 (0.42)	
Transmission modes		0.654
Sexual activity	-0.45 (0.43)	
Others	-0.49 (0.33)	
Body Mass Index		0.520
Underweight	-0.49 (0.33)	
Normal/healthy weight	-0.46 (0.40)	
Overweight/ obese	-0.43 (0.46)	
Depression	0.07	**0.019***
Anxiety	0.03	0.260

Note: *SD*: Standard deviation; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. All variables were selected at baseline assessment.

Table 5.8 Bivariate analysis of the change (slope) in HRQoL

Variables	**Slope of HRQoL** ***r* or mean (*SD*)**	***p*-value**
Age in years	-0.01	0.699
Time since HIV diagnosis in years	-0.01	0.871
Duration of ART in years	0.01	0.767
Gender		0.448
Male	-0.03 (0.87)	
Female	-0.04 (0.93)	
Marital status		**0.001****
Single/separated	0.05 (0.83)	
Married/cohabitated	-0.11 (0.91)	
Divorced/widowed	0.12 (0.97)	
Ethnicity		0.102
Han	-0.07 (0.90)	
Non-Han	0.03 (0.87)	
Types of residence		0.413
City	-0.02 (0.88)	
County	0.02 (0.87)	
Rural	-0.08 (0.93)	
Education attainment		0.078
Less than or equal to middle school	-0.06 (0.93)	
High school or above	0.01 (0.83)	
Employment		0.096
Unemployed	0.09 (1.04)	
Part time	0.03 (0.93)	
Full time	-0.09 (0.83)	
Levels of monthly income		0.291
No more than 1,999 RMB	0.03 (0.97)	
2,000 ~ 3,999 RMB	-0.06 (0.89)	
At least 4,000 RMB	-0.09 (0.78)	
Transmission modes		**<0.001*****
Sexual activity	-0.09 (0.88)	
Others	0.09 (0.92)	
Body Mass Index		0.357
Underweight	-0.13 (0.89)	
Normal/healthy weight	-0.03 (0.89)	
Overweight/obese	0.03 (0.91)	
Depression	0.34	**<0.001*****
Anxiety	0.35	**<0.001*****

Note: *SD*: Standard deviation; *: p <0.05; **: p < 0.01; ***: p < 0.001. All variables were selected at baseline assessment.

Table 5.9 Model fits of path models

Models	χ^2 **value**	χ^2/df	***p*-value**	***RMSEA***	***CFI***	***TLI***	***SRMR***
CD4 count							
Original model	2042.024	11.282	<0.001	0.093	0.665	0.654	0.090
Model trimming	1887.032	15.218	<0.001	0.109	0.678	0.657	0.108
Final model	523.066	5.506	<0.001	0.061	0.922	0.891	0.062
Viral suppression							
Original model	1695.716	18.841	<0.001	0.122	0.763	0.711	0.111
Model trimming	1704.493	17.393	<0.001	0.117	0.763	0.734	0.111
Final model	456.600	5.248	<0.001	0.060	0.946	0.924	0.059
HRQoL							
Original model	3267.940	23.014	<0.001	0.138	0.476	0.432	0.154
Model trimming	3227.936	26.900	<0.001	0.148	0.481	0.429	0.168
Final model	527.293	6.760	<0.001	0.069	0.926	0.876	0.065

Note: HRQoL: Health-related quality of life.

Table 5.10 Path coefficients (CD4 count)

Paths	***β***	***Std.β***	***95% CI***	***SE***	***p-value***
IS ---» ARTS	-0.114	-0.127	-0.170~-0.058	0.029	**<0.001*****
AS ---» ARTS	-0.123	-0.131	-0.177~-0.070	0.027	**<0.001*****
ES ---» ARTS	-0.197	-0.133	-0.278~-0.116	0.041	**<0.001*****
IS ---» ARTM	-0.012	-0.041	-0.030~0.006	0.009	0.199
AS ---» ARTM	-0.062	-0.199	-0.080~-0.044	0.009	**<0.001*****
ES ---» MED	-0.057	-0.055	-0.096~-0.018	0.020	**0.005****
ARTS ---» MED	0.066	0.095	0.039~0.092	0.014	**<0.001*****
ARTM ---» MED	0.079	0.038	0.002~0.157	0.040	**0.045***
MED ---» CD4 count	-0.058	-0.038	-0.111~-0.004	0.027	**0.034***

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; *CI*: Confidence interval; *SE*: Standard error; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 5.11 Results of longitudinal mediation analysis (CD4 count)

Effects	***β***	***Std.β***	***95% CI***	***SE***	***p-value***
From IS to CD4 count					
Indirect effect					
IS ---» ARTS ---» MED ---» CD4 count	0.000	0.000	0.000~0.001	0.000	0.094
IS ---» ARTM ---» MED ---» CD4 count	0.000	0.000	0.000~0.000	0.000	0.431
From AS to CD4 count					
Indirect effect					
AS ---» ARTS ---» MED ---» CD4 count	0.000	0.000	0.000~0.001	0.000	0.076
AS ---» ARTM ---» MED---» CD4 count	0.000	0.000	0.000~0.001	0.000	0.175
From ES to CD4 count					
Indirect effect					
ES ---» MED ---» CD4 count	0.003	0.002	0.000~0.009	0.002	0.106
ES ---» ARTS ---» MED ---» CD4 count	0.001	0.000	0.000~0.002	0.000	0.082
From IS to MED					
Indirect effect					
IS ---» ARTS ---» MED	-0.007	-0.012	-0.014~-0.003	0.002	**0.002****
IS ---» ARTM ---» MED	-0.001	-0.002	-0.004~0.000	0.001	0.328
From AS to MED					
Indirect effect					
AS ---» ARTS ---» MED	-0.008	-0.012	-0.013~-0.004	0.002	**0.001*****
AS ---» ARTM ---» MED	-0.005	-0.008	-0.011~0.000	0.003	0.057
From ES to MED					
Indirect effect					
ES ---» ARTS ---» MED	-0.013	-0.013	-0.021~-0.006	0.004	**0.001*****
Direct effect	-0.057	-0.055	-0.097~-0.019	0.020	**0.005****

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; *CI*: Confidence interval; *SE*: Standard error; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 5.12 Path coefficients (Viral suppression)

Paths	***β***	***Std.β***	***95% CI***	***SE***	***p-value***
IS ---» ARTS	-0.112	-0.125	-0.167~-0.056	0.028	**<0.001*****
AS ---» ARTS	-0.123	-0.130	-0.176~-0.069	0.027	**<0.001*****
ES ---» ARTS	-0.196	-0.133	-0.277~-0.115	0.041	**<0.001*****
IS ---» ARTM	-0.012	-0.040	-0.030~0.007	0.009	0.210
AS ---» ARTM	-0.061	-0.196	-0.079~-0.043	0.009	**<0.001*****
ES ---» MED	-0.056	-0.055	-0.095~-0.017	-0.056	**0.005****
ARTS ---» MED	0.066	0.095	0.039~0.093	0.066	**<0.001*****
ARTM ---» MED	0.080	0.038	0.002~0.157	0.080	**0.045***
MED ---» VS	-0.035	-0.032	-0.058~-0.012	-0.035	**0.003****

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; VS: Viral suppression; *CI*: Confidence interval; *SE*: Standard error; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 5.13 Results of longitudinal mediation analysis (Viral suppression)

Effects	***β***	***Std.β***	***95% CI***	***SE***	***p-value***
From IS to VS					
Indirect effect					
IS ---» ARTS ---» MED ---» VS	0.000	0.000	0.000~0.001	0.000	**0.034***
IS ---» ARTM ---» MED ---» VS	0.000	0.000	0.000~0.000	0.000	0.387
From AS to VS					
Indirect effect					
AS ---» ARTS ---» MED ---» VS	0.000	0.000	0.000~0.001	0.000	**0.023***
AS ---» ARTM ---» MED---» VS	0.000	0.000	0.000~0.000	0.000	0.123
From ES to VS					
Indirect effect					
ES ---» MED ---» VS	0.002	0.002	0.000~0.005	0.001	0.053
ES ---» ARTS ---» MED ---» VS	0.000	0.000	0.000~0.001	0.000	**0.034***
From IS to MED					
Indirect effect					
IS ---» ARTS ---» MED	-0.007	-0.012	-0.013~-0.003	0.002	**0.003****
IS ---» ARTM ---» MED	-0.001	-0.002	-0.004~0.000	0.001	0.336
From AS to MED					
Indirect effect					
AS ---» ARTS ---» MED	-0.008	-0.012	-0.013~-0.004	0.002	**0.001*****
AS ---» ARTM ---» MED	-0.005	-0.007	-0.010~0.000	0.003	0.058
From ES to MED					
Indirect effect					
ES ---» ARTS ---» MED	-0.013	-0.013	-0.021~-0.006	0.004	**0.001****
Direct effect	-0.056	-0.055	-0.097~-0.019	0.020	**0.005****

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; VS: Viral suppression; *CI*: Confidence interval; *SE*: Standard error; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 5.14 Path coefficients (Health-related quality of life)

Paths	***β***	***Std.β***	***95% CI***	***SE***	***p-value***
IS ---» ARTS	-0.126	-0.140	-0.182~-0.069	0.026	**<0.001*****
AS ---» ARTS	-0.121	-0.128	-0.174~-0.067	0.027	**<0.001*****
ES ---» ARTS	-0.211	-0.143	-0.293~-0.129	0.040	**<0.001*****
IS ---» ARTM	-0.007	-0.022	-0.025~0.012	0.008	0.431
AS ---» ARTM	-0.062	-0.199	-0.080~-0.044	0.009	**<0.001*****
ES ---» MED	-0.053	-0.052	-0.092~-0.014	0.018	**0.003****
ARTS ---» MED	0.065	0.094	0.038~0.092	0.012	**<0.001*****
ARTM ---» MED	0.087	0.041	0.009~0.164	0.037	**0.019***
IS ---» HRQoL	-0.184	-0.128	-0.264~-0.104	0.038	**<0.001*****
ES ---» HRQoL	-0.302	-0.127	-0.431~-0.173	0.060	**<0.001*****
ARTS ---» HRQoL	0.386	0.241	0.297~0.475	0.041	**<0.001*****
ARTM ---» HRQoL	0.999	0.204	0.749~1.248	0.121	**<0.001*****

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; HRQoL: Health-related quality of life; *CI*: Confidence interval; *SE*: Standard error; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 5.15 Results of longitudinal mediation analysis (HRQoL)

Effects	***β***	***Std.β***	***95% CI***	***SE***	***p-value***
From IS to HRQoL					
Indirect effect					
IS ---» ARTS ---» HRQoL	-0.049	-0.034	-0.074~-0.023	0.013	**<0.001*****
IS ---» ARTM ---» HRQoL	-0.007	-0.005	-0.025~0.012	0.009	0.482
Direct effect	-0.184	-0.128	-0.264~-0.104	0.041	**<0.001*****
From AS to HRQoL					
Indirect effect					
AS ---» ARTS ---» HRQoL	-0.047	-0.031	-0.070~-0.023	0.012	**<0.001*****
ARTS ---» ARTM ---» HRQoL	-0.062	-0.041	-0.086~-0.037	0.012	**<0.001*****
From ES to HRQoL					
Indirect effect					
ES ---» ARTS ---» HRQoL	-0.082	-0.034	-0.119~-0.044	0.019	**<0.001*****
Direct effect	-0.302	-0.127	-0.431~-0.173	0.066	**<0.001*****
From IS to MED					
Indirect effect					
IS ---» ARTS ---» MED	-0.008	-0.013	-0.013~-0.003	0.003	**0.001****
IS ---» ARTM ---» MED	-0.001	-0.001	-0.002~0.001	0.001	0.539
From AS to MED					
Indirect effect					
AS ---» ARTS ---» MED	-0.008	-0.012	-0.012~-0.003	0.002	**0.001****
AS ---» ARTM ---» MED	-0.005	-0.008	-0.010~0.000	0.003	**0.040***
From ES to MED					
Indirect effect					
ES ---» ARTS ---» ARTM	-0.014	-0.013	-0.022~-0.006	0.004	**0.001****
Direct effect	-0.053	-0.052	-0.092~-0.014	0.020	**0.008****

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; HRQoL: Health-related quality of life; *CI*: Confidence interval; *SE*: Standard error; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

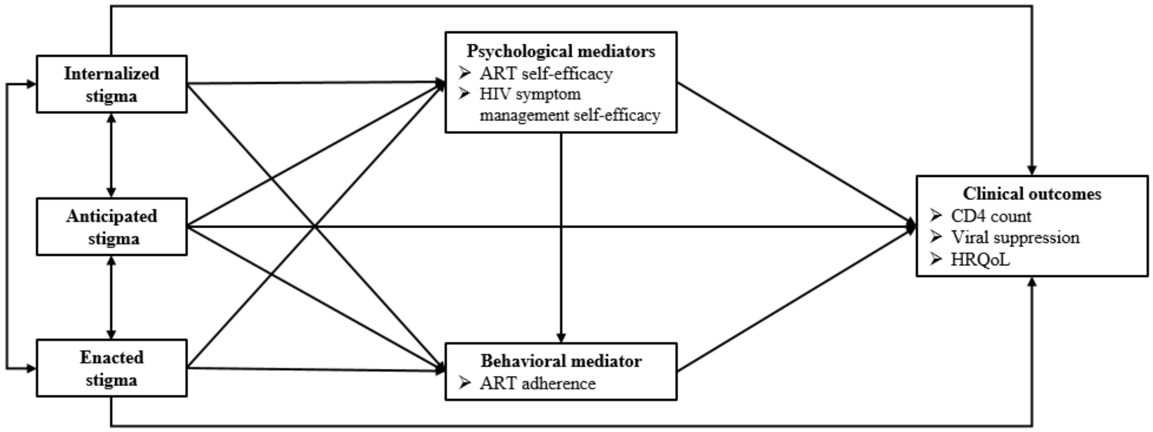

Figure 5.1 Conceptual model

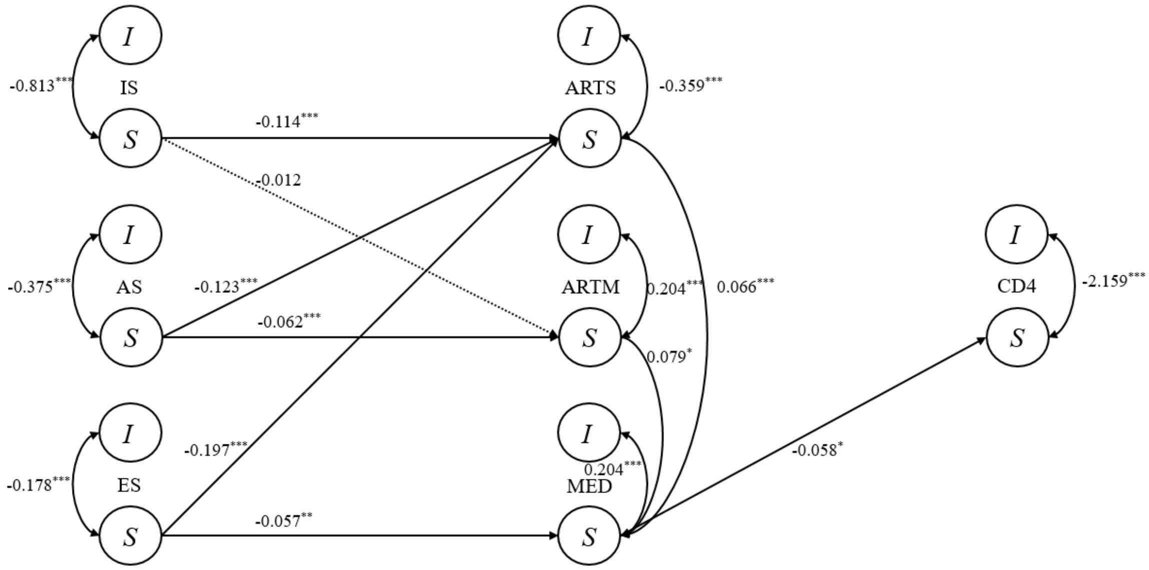

Figure 5.2 Final path model of CD4 count

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; Covariates, such as duration of ART, depression, anxiety, were controlled in this model. All pathways in modification indices were omitted in this model but could be found in the Appendix D.

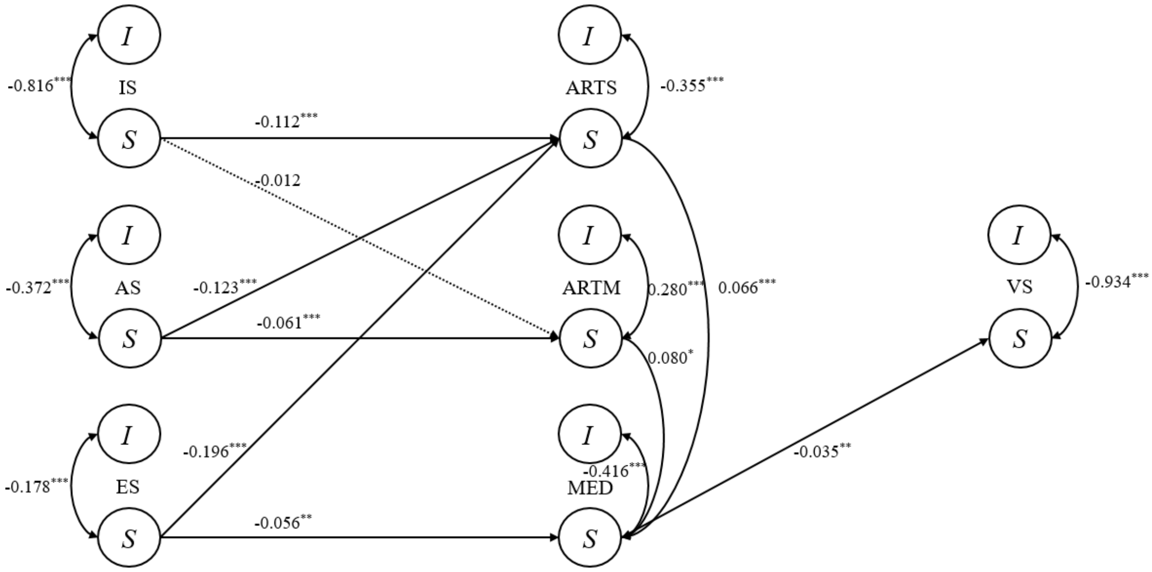

Figure 5.3 Final path model of viral suppression

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; VS: Viral suppression; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; Covariates, such as duration of ART, depression, anxiety, were controlled in this model. All pathways in modification indices were omitted in this model but could be found in the Appendix D.

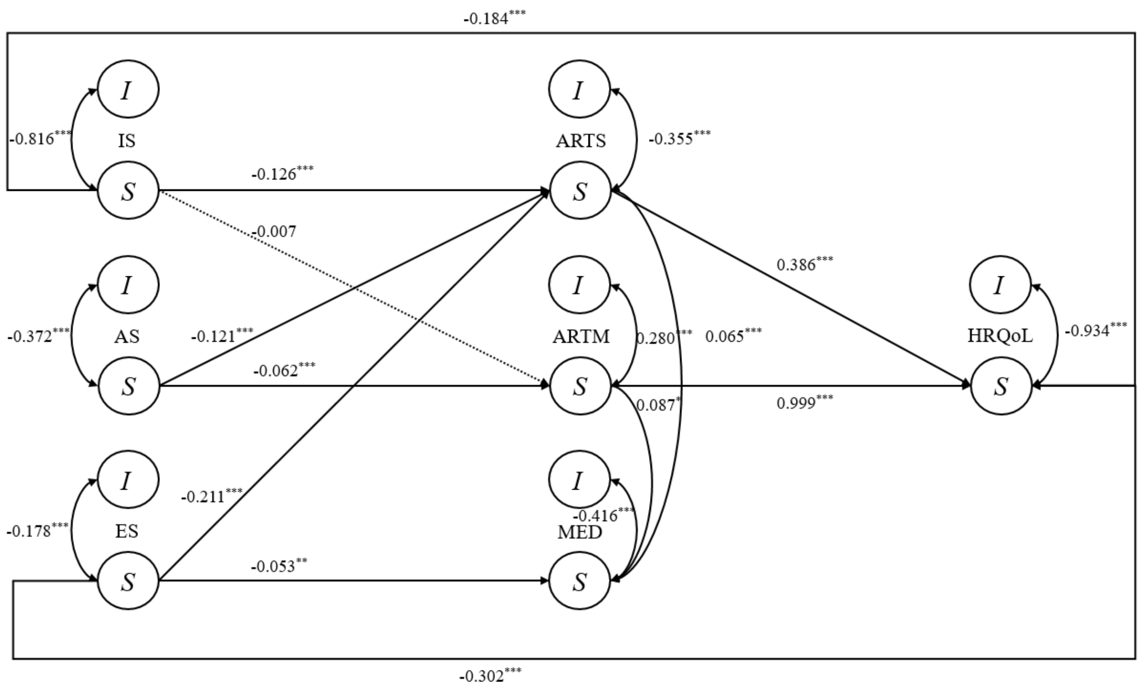

Figure 5.4 Final path model of HRQoL

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; HRQoL: Health-related quality of life; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; Covariates, such as time since HIV diagnosis, depression, anxiety, baseline CD4 count, were controlled in this model. All pathways in modification indices were omitted in this model but could be found in the Appendix D.

CHAPTER 6

DISCUSSION

6.1 Summary of the dissertation

Leveraging data derived from a prospective cohort study and longitudinal analytic approach, this dissertation aims to investigate two research questions: 1) the impacts of HIV-related stigma on clinical outcomes after accounting for psycho-behavioral factors and covariates; and 2) the psycho-behavioral mechanisms underlying HIV-related stigma and clinical outcomes among PLWH in Guangxi, China. The findings generating from this dissertation partially confirmed the hypotheses and had important implication for research and practices. This chapter summarizes the research findings first. Then, the strengths and limitations of this dissertation are discussed. Moreover, this chapter gives detailed discussion to the implication of research findings and future direction for stigma research as well as intervention. Finally, it presents key research conclusions based on the findings.

Using hierarchical longitudinal analytic approach, Study 1 explored whether internalized, anticipated, and enacted stigma had different impacts on the three clinical outcomes (i.e., CD4, viral suppression, HRQoL) after accounting for psycho-behavioral factors and sociodemographic characteristics. The results revealed that the three types of HIV-related stigma could explain additional variance of each clinical outcome. Internalized, anticipated, and enacted stigma were negatively associated with HRQoL but not with CD4 count and viral suppression. Psycho-behavioral factors could explain large variance of clinical outcomes, and some of their impacts changed after adding HIV-related stigma to the model. These findings implied that 1) HIV-related stigma might have different impacts on different clinical outcomes; 2) psycho-behavioral factors might mediate the relationship between stigma and clinical outcomes; 3) these psycho-behavioral mechanisms might be different by each type of stigma and clinical outcomes.

Based on the findings in Study 1, Study 2 employed longitudinal mediation analysis to examine the psycho-behavioral mechanisms of HIV-related stigma on clinical outcomes. None of the three types of stigma had direct impacts on CD4 count and viral suppression, but the direct impacts of internalized and enacted stigma were found in HRQoL. The psycho-behavioral mechanisms were also different by each type of HIV-related stigma and clinical outcomes. Treatment-related self-efficacy (i.e., ART self-efficacy, HIV symptom management self-efficacy) and ART adherence could mediate the indirect pathways from HIV-related stigma to viral suppression but these effects were not found in CD4 count. The serial mediating effects from HIV-related stigma, ART self-efficacy, ART adherence to viral suppression were different by baseline CD4 count. ART self-efficacy could consistently mediate the impacts of three stigma on HRQoL but the mediating effect of HIV symptom management self-efficacy was only found in the pathway between anticipated stigma and HRQoL. Across the three types of HIV-related stigma, ART self-efficacy could consistently mediate their impacts on ART adherence. Similarly, only anticipated stigma could affect ART adherence through reducing HIV symptom management self-efficacy. These findings confirmed Earnshaw and her colleagues' hypotheses which emphasized the potentially distinct mechanisms of internalized, anticipated, and enacted stigma on clinical outcomes (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013). Additionally, this study added value to prior research by confirming the mechanisms of psychological resources. Finally, this study suggested that future stigma research should consider the characteristics of each type of HIV-related stigma and clinical outcome and use these knowledge to frame the pathways between them.

6.2 Strengths and limitations

Strengths

This dissertation has several strengths. First, data used in this dissertation were derived from the four-wave assessment in a prospective cohort among PLWH in Guangxi, China. The high quality longitudinal data and low attrition rates across the time ensured that this dissertation had strong ability for causal inference as compared to the previous studies in cross sectional design (Earnshaw et al., 2013; Logie et al., 2019; Rao et al., 2012; Rao et al., 2019; Turan, Budhwani, et al., 2017; Turan et al., 2016). Second, participants in the cohort were vulnerable to HIV-related stigma as most of them from rural areas, had low SES, and experienced the influences of traditional culture and local HIV epidemic (Li et al., 2015; Wang, 2013; Yang et al., 2019). Third, in addition to immunologic and virologic outcomes, this dissertation emphasized the importance of HRQoL which could give comprehensive assessment to health quality (Ashing-Giwa, 2005; Ruiz Perez et al., 2005; Wu et al., 1997).

Fourth, in the contrast to existing studies which predominantly focused on the overall HIV-related stigma or one or more types (Fuster-Ruizdeapodaca et al., 2014; Logie et al., 2019; Parcesepe et al., 2020), this dissertation considered the three common types of HIV-related stigma simultaneously and investigated their separate impacts and mechanisms on clinical outcomes. Fifth, as suggested by Turan and his colleagues (Turan, Hatcher, et al., 2017), psychological resources are important mechanisms between HIV-related stigma and health outcomes. Therefore, this dissertation incorporated ART self-efficacy and HIV symptom management self-efficacy into conceptual framework and investigated whether they could mediate the pathways between stigma and clinical outcomes. Finally, leveraging LGCM and longitudinal mediation analysis, the second study of this dissertation explored how the changes of HIV-related influenced those of clinical outcomes through psycho-behavioral pathways. These methods and results could provide robust research evidence to support the causality between stigma and health outcomes and confirm the mediating roles of ART self-efficacy, HIV symptom management self-efficacy, and ART adherence.

Limitations

Besides the strengths, there were some limitations that need to be acknowledged. First, the cohort study was conducted in clinical settings/hospitals, which might result in better health outcomes among participants. Additionally, as compared with PLWH who did not engage in care or seek help in clinics, the participants in this dissertation might have lower HIV-related stigma and higher treatment-related self-efficacy, which might also threaten the internal and external validity of our findings. For instance, there were more than 70% of the PLWH without stigmatized experiences in the last 6 months. Future studies with diverse PLWH recruited from both clinics and other settings are needed. Second, due to age-related issues, PLWH who were older than 60 years were excluded from the cohort study. However, as compared to young adults, older PLWH may experience higher levels of HIV-related stigma and often engage in maladaptive stigma management strategies (e.g., non-disclosure and suboptimal ART adherence), which may also result in suboptimal clinical outcomes (Emlet, 2014). Third, only four-wave datasets were used in this dissertation, which might limit the ability to see significant changes among variables of interest and confirm the causality among them. Fourth, self-report measures were employed to evaluate variables of interest, which might result in self-reported bias. For instance, the ART adherence in this dissertation might be overestimated because of social desirability bias even though we used a multiple-item approach to assess the variable (Stirratt et al., 2015). To improve the validity of adherence measurement and assess adherence adequately, objective measurement tools, such as biomarkers and device-based measurement, are needed. Additionally, due to social desirability bias, the stigmatized experiences might be underestimated in Study 2. Future studies are needed to improve the validity of this measure. Fifth, this dissertation only focused on three common types of HIV-related stigma, such as internalized, anticipated, and enacted stigma. However, there are also other types of HIV-related stigma, such as disclosure concerns and concern with public attitudes toward PLWH, which were defined by other stigma measurement tools and used in previous studies but were not included in this dissertation (Abdul Bari, 2017; Berger et al., 2001). These types of HIV-related stigma may also influence clinical outcomes through different psycho-behavioral mechanisms. For instance, the measure of internalized stigma was derived from the HIV Stigma Scale which also captures disclosure concerns (Berger et al., 2001). The disclosure concerns may influence clinical outcomes through impeding disclosure behaviors among PLWH and limiting their resource access (Omarzu, 2000; Qiao, Li, & Stanton, 2013).

Sixth, although this dissertation emphasized the importance of psychological resources and used treatment-related self-efficacy to reflect them, other psychological resources, such as resilience, positive coping, and avoid coping, may also mediate the relationship between stigma and clinical outcomes (Turan, Hatcher, et al., 2017). Future studies are needed to investigate their mediating roles. Seventh, as CD4 count and viral load were categorized as binary variables based on the clinical implication in immunologic recovery and viral suppression, only limited information of these two outcomes were used in the data analysis. Eighth, due to study design, some of the sociodemographic characteristics, such as levels of monthly income and marital status, were only collected at baseline. However, these characteristics may change during the follow-ups, have time-varying effects on health outcomes, and thus should be controlled in future research. Ninth, survey approach was employed to investigate the research hypotheses in this dissertation. However, in the contrast to quantitative study, qualitative studies could obtain a comprehensive picture of the cultural context and give better understanding of the complex mechanisms of HIV-related stigma on clinical outcomes. Finally, the cohort study was conducted in Guangxi, China, cautions are needed when generalizing the findings from this dissertation to other areas of China, other cultural settings, or other countries.

6.3 Implications

This dissertation has important implications for both HIV-related stigma research and practices. From the research perspective, the significant direct and indirect impacts of

HIV-related stigma on HRQoL suggested that HIV-related stigma might not only influence immunologic and virologic outcomes but also impair the overall health quality of PLWH. In addition to immunologic and virologic outcomes, future stigma research are called for investigating its mechanisms on HRQoL among PLWH, especially for those under treatment as they need to cope with the challenges (e.g., drug side effects, opportunistic infections, mental health problems) besides immunologic recovery and viral suppression (Lazarus et al., 2016). Moreover, the differential direct and indirect impacts of internalized, anticipated, and enacted stigma on the three clinical outcomes suggested that the mechanisms of them on clinical outcomes might be different (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013). Research only focusing on overall HIV-related stigma or one or more type may ignore the nuanced differences among them and may not inform effective interventions to alleviate their impacts on clinical outcomes. Furthermore, the significant mediating roles of psychological resources between stigma and health outcomes implied that they are an important psychological mechanism besides psychological distress, such as depression and anxiety (Turan, Hatcher, et al., 2017). The investigation on their mediating roles could inform future positive psychology interventions which could buffer the negative impacts of stigma. Finally, the application of latent growth curve modelling and longitudinal mediation analysis in this dissertation could examine the pathways among the changes of key variables rather than the associations of mean values (Cheong et al., 2003). Therefore, findings in this dissertation have implication in promoting the future application of these approach to examine mechanisms from a longitudinal perspective.

Regarding to the implication for practical interventions, interventions aiming to promote clinical outcomes should target both HIV-related stigma and psycho-behavioral mediators. As internalized, anticipated, and enacted stigma may influence clinical outcomes through different mechanisms, effective stigma interventions should be tailored to their characteristics. For instance, internalized and anticipated stigma reflect the negative cognition process and beliefs at the intrapersonal level, which might result in the mental health disorders, risk behaviors, and suboptimal clinical outcomes among PLWH (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013). Individual interventions targeting internalized and anticipated stigma, such as psychological counselling and resilience-based interventions (e.g., coping strategies, emotion regulation, stress management), could alleviate their negative impacts (Rao et al., 2019). In contrast, enacted stigma represents the actual stigmatized experiences from others or in the public. Hence, structural interventions, such as public health education and public campaigns, may reduce the misunderstanding and discrimination against PLWH (Rao et al., 2019). Additionally, as the conservative social culture in China is one of the causes of HIV-related stigma, structural interventions targeting the social culture and correcting the misinformation about HIV may be effective in reducing the HIV-related stigma at the intrapersonal level or in the social environment (Auerbach, 2009). In this dissertation, as we found that HIV-related stigma had direct impacts on the HRQoL, structural interventions targeting the social culture may be also effective in improving the overall health quality among PLWH.

Interventions should be also tailored to different clinical outcomes. For example, as all three types of HIV-related stigma could impair HRQoL directly, the aforementioned stigma reduction interventions could improve HRQoL effectively. However, since stigma could only influence CD4 count and viral suppression indirectly, intervention should also target the psycho-behavioral mechanisms besides HIV-related stigma. The significant mediating effects of treatment-related self-efficacy suggested that interventions promoting confidence and motivation to health behaviors, such as skill training, self-management, and problem-solving, might be effective in buffering the negative influences of HIV-related stigma, maintaining treatment-related behaviors, and improving clinical outcomes (Areri, Marshall, & Harvey, 2020). As PLWH with optimal clinical outcomes may have low perception of disease severity which may result in suboptimal ART adherence, missed medical appointments, and health outcomes, behavioral interventions, such as daily reminder and self-management, are also needed to maintain or improve adherence behaviors (Gao, Nau, Rosenbluth, Scott, & Woodward, 2000; Guo et al., 2020a; Spire et al., 2002).

6.4 Future direction

Future direction for both research design and implementation are needed to improve the quality of this dissertation and confirm its research findings. From the perspective of research design, prospective cohort design could provide high quality longitudinal data which are helpful to examine the causality between stigma and clinical outcomes. Additionally, long-term follow-ups embedded in prospective cohort study could allow us to capture the significant changes among variables of interest and test the associations. What is more, participants recruited from both clinics and other settings (e.g., community) may have differences in key variables and could provide rich information for causal inference. Furthermore, the improvement of measurement tools among key variables, such as ART adherence and enacted stigma, could capture their information accurately and ensure the findings have good internal validity. For example, the antiretroviral concentration in biological samples (e.g., hair, saliva, blood) among PLWH may be an objective indicator of ART adherence and could avoid the influence of self-report bias (Zhang, Qiao, Yang, & Li, 2020). Finally, the significant impacts of some sociodemographic characteristics, such as marital status, levels of monthly income, and types of residence, on clinical outcomes implied that they might have different impacts on HIV-related stigma and health outcomes over time. During research design and data collection, the time-varying effects of these variables should be considered and assessed.

In terms of implementation-related research, some future direction regarding research ideas and data analysis could provide comprehensive information and justification of the findings in this dissertation. First, besides HIV-related stigma, PLWH in Guangxi may suffer from other types of stigma, such as stigma related to poverty, sexual identity, and gender (Ghiasvand et al., 2020; Turan, Hatcher, et al., 2017), which were not examined in this dissertation. The intersectionality of these stigma reflects the multiple interlocking systems of privilege and oppression at macro, social-structural level, and influence clinical outcomes through complex pathways (Bowleg, 2012; Collins, 2015; Ghiasvand et al., 2020). The investigation of intersecting stigma could provide additional picture of how the clinical outcomes of PLWH from different identities are influenced through the psycho-behavioral pathways (Turan, Hatcher, et al., 2017). These findings may inform future interventions tailored to PLWH of different identities, which could improve health outcomes effectively. Second, internalized, anticipated, and enacted stigma are three common types of HIV-related stigma used in prior research, but they may not influence clinical outcomes independently. Instead, they may interact with each other, form different profiles (e.g., high internalized and anticipated stigma but low enacted stigma), and affect clinical outcomes through different psycho-behavioral mechanisms (Earnshaw & Chaudoir, 2009; Earnshaw et al., 2013; Turan, Budhwani, et al., 2017; Turan, Hatcher, et al., 2017). The investigation on these profiles may elaborate the potentially distinct psycho-behavioral mechanisms better than the findings in the current dissertation or at least justify the current findings.

Third, HRQoL covers 11 dimensions, such as physical functioning, social functioning, cognitive functioning, pain, and mental health (Wu et al., 1997), but it was used as a composite score in this dissertation, which might ignore the plausible different mechanisms of HIV-related stigma on different dimensions of HRQoL. Future investigation on these mechanisms could uncover the complex pathways between stigma and different domains of HRQoL and provide empirical evidences to inform targeted interventions to improve the overall health quality among PLWH. Fourth, some sociodemographic or HIV infection characteristics, such gender, time since HIV diagnosis or infection stages, may moderate the mechanisms of clinical outcomes underlying HIV-related stigma. For example, Mahajan and colleagues suggested that PLWH in asymptomatic period might be less vulnerable to HIV-related stigma than those with symptoms as they did not have physical manifestations of HIV, had stable capability of maintaining daily routine, and were difficult to identify as different in the public (Mahajan et al., 2008). The different levels of HIV-related stigma by disease stages may influence their impacts on psychological and physical wellbeing among PLWH. Studies on these moderating effects or subgroup analysis by different sociodemographic characteristics could examine for whom under which disease stages, the conceptual model of this dissertation may work. These investigations could provide evidence for tailoring stigma reduction intervention to PLWH of different stages of infection.

6.5 Conclusion

Building from the Health Stigma Framework and prior research, this dissertation provided further investigation on the separate impacts and mechanisms of internalized, anticipated, and enacted stigma on clinical outcomes. In accordance with the Health Stigma Framework, different impacts and mechanisms of HIV-related stigma on clinical outcomes were detected. Psychological resources and ART adherence could mediate the pathways from stigma to clinical outcomes. Future studies are needed to examine these mechanisms among PLWH of different backgrounds in both clinics and community settings. Interventions aiming to improve clinical outcomes should be tailored to internalized, anticipated, and enacted stigma at both intrapersonal and interpersonal levels, target relevant psycho-behavioral pathways, promote the resilience, and maintain/improve the adherence behaviors of PLWH.

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APPENDIX A

CORRELATION STRUCTURE AND MODEL SELECTION

Table A.1 Model fit of generalized linear mixed model of CD4 count in Step 1

Models	Covariance	QIC	QICu
Model 1	Unstructured	5968.9531	5918.4927
Model 2	Autoregressive	5853.5086	5803.0767
Model 3	**Exchange**	**5851.2879**	**5800.5255**
Model 4	Independent	5852.5399	5798.7923

Table A.2 Model fit of generalized linear mixed model of CD4 count in Step 2

Models	Covariance	QIC	QICu
Model 1	Unstructured	5766.6410	5718.2486
Model 2	Autoregressive	5635.9332	5591.3602
Model 3	Exchange	5635.3364	5591.0257
Model 4	**Independent**	**5619.7931**	**5563.2591**

Table A.3 Model fit of generalized linear mixed model of CD4 count in Step 3

Models	Covariance	QIC	QICu
Model 1	Unstructured	5712.1213	5665.2957
Model 2	Autoregressive	5606.9331	5565.1331
Model 3	Exchange	5606.6371	5564.8352
Model 4	**Independent**	**5592.1565**	**5532.9077**

Table A.4 Model fit of generalized linear mixed model of viral suppression in Step 1

Models	**Covariance**	**QIC**	**QICu**
Model 1	Unstructured	1518.2168	1509.9828
Model 2	Autoregressive	1518.7922	1510.3066
Model 3	Exchange	1518.7236	1509.9804
Model 4	**Independent**	**1518.0639**	**1509.4087**

Table A.5 Model fit of generalized linear mixed model of viral suppression in Step 2

Models	**Covariance**	**QIC**	**QICu**
Model 1	Unstructured	1452.6661	1445.5917
Model 2	**Autoregressive**	**1452.3487**	**1444.7407**
Model 3	Exchange	1455.1258	1445.9396
Model 4	Independent	1453.6036	1442.9401

Table A.6 Model fit of generalized linear mixed model of viral suppression in Step 3

Models	**Covariance**	**QIC**	**QICu**
Model 1	Unstructured	1430.8067	1425.5541
Model 2	**Autoregressive**	**1430.1513**	**1424.1176**
Model 3	Exchange	1432.9292	1424.6779
Model 4	Independent	1431.5986	1420.7865

Table A.7 Model fit of generalized linear mixed model of HRQoL in Step 1

Models	Covariance	-2 Res Log Likelihood	AIC	AICC	BIC
Model 1	**Unstructured**	**34365.3**	**34369.3**	**34369.3**	**34379.4**
Model 2	Compound symmetry	34365.3	34371.3	34371.3	34386.5
Model 3	Heterogeneous compound symmetry	34365.3	34371.3	34371.3	34386.5
Model 4	Autoregressive	34365.3	34371.3	34371.3	34386.5
Model 5	Heterogeneous autoregressive	34365.3	34371.3	34371.3	34386.5

Table A.8 Model fit of generalized linear mixed model of HRQoL in Step 2

Models	Covariance	-2 Res Log Likelihood	AIC	AICC	BIC
Model 1	**Unstructured**	**30165.1**	**30169.1**	**30169.1**	**30179.3**
Model 2	Compound symmetry	30165.1	30171.1	30171.1	30186.4
Model 3	Heterogeneous compound symmetry	30165.1	30171.1	30171.1	30186.4
Model 4	Autoregressive	30165.1	30171.1	30171.1	30186.4
Model 5	Heterogeneous autoregressive	30165.1	30171.1	30171.1	30186.4

Table A.9 Model fit of generalized linear mixed model of HRQoL in Step 3

Models	Covariance	-2 Res Log Likelihood	AIC	AICC	BIC
Model 1	**Unstructured**	**29812.7**	**29816.7**	**29816.7**	**29826.9**
Model 2	Compound symmetry	29812.7	29818.7	29818.7	29834.0
Model 3	Heterogeneous compound symmetry	29812.7	29818.7	29818.7	29834.0
Model 4	Autoregressive	29812.7	29818.7	29818.7	29834.0
Model 5	Heterogeneous autoregressive	29812.7	29818.7	29818.7	29834.0

APPENDIX B

SUBGROUP ANALYSIS OF CD4 COUNT

Table B.1 Hierarchical generalized linear mixed model of CD4 count among PLWH under 45 years old

Variables	***AOR* (95% *CI*)**		
	Model 1 (*n*=824)	**Model 2 (*n*=788)**	**Model 3 (*n*=782)**
Step 1: Sociodemographic characteristics			
Time	1.04 (0.99~1.08)	**1.05 (1.00~1.10)***	**1.05 (1.00~1.10)***
Age in years	**0.69 (0.55~0.86)*****	**0.70 (0.56~0.87)****	**0.69 (0.55~0.87)****
Duration of ART in years	**1.17 (1.02~1.35)***	**1.21 (1.04~1.40)***	**1.21 (1.04~1.40)***
Gender			
Male	**0.69 (0.51~0.93)***	**0.68 (0.50~0.92)***	**0.68 (0.51~0.92)***
Female		Reference	
Marital status			
Single/separated	1.06 (0.77~1.46)	1.06 (0.77~1.47)	1.05 (0.76~1.45)
Married/cohabitated		Reference	
Divorced/widowed	0.84 (0.54~1.29)	0.84 (0.54~1.30)	0.85 (0.55~1.32)
Ethnicity			
Han	0.87 (0.68~1.11)	0.86 (0.67~1.11)	0.87 (0.67~1.12)
Non-Han		Reference	
Types of residence			
City	**1.77 (1.30~2.41)*****	**1.65 (1.21~2.26)****	**1.67 (1.22~2.29)****
County	**1.62 (1.15~1.29)****	**1.51 (1.06~2.14)***	**1.51 (1.06~2.15)***

Rural		Reference	
Education attainment			
Less than or equal to middle school		Reference	
High school or above	1.25 (0.94~1.67)	1.25 (0.93~1.67)	1.22 (0.91~1.63)
Levels of monthly income			
No more than 1,999 Yuan		Reference	
2,000 ~ 3,999 Yuan	0.91 (0.69~1.22)	0.92 (0.69~1.23)	0.91 (0.68~1.21)
At least 4,000 Yuan	1.20 (0.83~1.73)	1.17 (0.80~1.70)	1.13 (0.78~1.65)
Transmission modes			
Sexual activity	0.88 (0.67~1.15)	0.88 (0.67~1.16)	0.88 (0.66~1.16)
Others		Reference	
Body Mass Index			
Underweight	**0.57 (0.43~0.74)*****	**0.71 (0.53~0.95)***	**0.72 (0.53~0.96)***
Normal/healthy weight		Reference	
Overweight/obese	**1.41 (1.09~1.82)****	**1.45 (1.01~2.07)***	**1.46 (1.02~2.10)***
Step 2: Psycho-behavioral factors			
ART self-efficacy		0.98 (0.88~1.08)	0.98 (0.88~1.08)
HIV symptom management self-efficacy		**1.21 (1.09~1.34)****	**1.22 (1.10~1.36)*****
Depression		**0.88 (0.77~0.99)***	**0.87 (0.76~0.99)***
Anxiety		**1.16 (1.02~1.33)***	**1.16 (1.02~1.33)***
ART adherence (*n*, %)			
Optimal		0.93 (0.74~1.16)	0.92 (0.74~1.15)
Suboptimal		Reference	
Step 3: HIV-related stigma			
Internalized stigma			0.98 (0.88~1.09)
Anticipated stigma			1.07 (0.97~1.20)
Enacted stigma			0.98 (0.89~1.08)
Pseudo R^2	0.115	0.159	0.165
ΔR2	-	0.042	0.006

Note: *AOR*: Adjusted odds ratio; *CI*: Confidence interval; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table B.2 Hierarchical generalized linear mixed model of CD4 count among PLWH older than 45 years

Variables	***AOR* (95% *CI*)**		
	Model 1 (*n*=295)	**Model 2 (*n*=286)**	**Model 3 (*n*=283)**
Step 1: Sociodemographic characteristics			
Time	1.03 (0.95~1.12)	1.06 (0.97~1.15)	**1.05 (0.96~1.14)**
Age in years	0.89 (0.52~1.50)	0.89 (0.52~1.54)	**0.92 (0.53~1.57)**
Duration of ART in years	1.19 (0.96~1.49)	1.21 (0.97~1.51)	**1.22 (0.98~1.53)**
Gender			
Male	**0.44 (0.27~0.71)*****	**0.44 (0.27~0.72)*****	**0.45 (0.28~0.73)****
Female		Reference	
Marital status			
Single/separated	1.84 (0.81~4.20)	1.79 (0.80~4.05)	1.77 (0.78~4.02)
Married/cohabitated		Reference	
Divorced/widowed	0.81 (0.46~1.43)	0.81 (0.46~1.42)	0.80 (0.46~1.41)
Ethnicity			
Han	**0.53 (0.33~0.86)****	**0.49 (0.30~0.79)****	**0.48 (0.29~0.77)****
Non-Han		Reference	
Types of residence			
City	1.17 (0.67~2.05)	1.18 (0.67~2.09)	1.17 (0.66~2.06)
County	1.32 (0.67~2.61)	1.46 (0.73~2.93)	1.46 (0.73~2.90)
Rural		Reference	
Education attainment			
Less than or equal to middle school		Reference	
High school or above	1.32 (0.72~2.40)	1.23 (0.68~2.24)	1.23 (0.67~2.23)
Levels of monthly income			
No more than 1,999 Yuan		Reference	
2,000 ~ 3,999 Yuan	**1.70 (1.03~2.81)***	1.64 (0.99~2.71)	**1.67 (1.01~2.75)***
At least 4,000 Yuan	1.29 (0.61~2.73)	1.38 (0.65~2.93)	1.40 (0.66~2.96)
Transmission modes			
Sexual activity	0.74 (0.44~1.26)	0.76 (0.45~1.30)	0.79 (0.47~1.33)
Others		Reference	

Body Mass Index			
Underweight	0.56 (0.30~1.05)	1.01 (0.47~2.21)	1.00 (0.46~2.20)
Normal/healthy weight		Reference	
Overweight/obese	1.08 (0.75~1.56)	1.34 (0.79~2.29)	1.31 (0.76~2.24)
Step 2: Psycho-behavioral factors			
ART self-efficacy		1.09 (0.90~1.31)	1.11 (0.92~1.34)
HIV symptom management self-efficacy		1.01 (0.83~1.22)	1.04 (0.85~1.26)
Depression		1.19 (0.96~1.48)	1.13 (0.90~1.41)
Anxiety		1.05 (0.83~1.32)	1.07 (0.85~1.35)
ART adherence (*n*, %)			
Optimal		1.17 (0.74~1.84)	1.11 (0.71~1.75)
Suboptimal		Reference	
Step 3: HIV-related stigma			
Internalized stigma			1.14 (0.95~1.38)
Anticipated stigma			1.05 (0.87~1.27)
Enacted stigma			1.01 (0.85~1.20)
Pseudo R^2	0.118	0.147	0.155
ΔR^2	-	0.029	0.008

Note: *AOR*: Adjusted odds ratio; *CI*: Confidence interval; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

APPENDIX C

ORIGINAL PATH MODELS

Table C.1 Original path model with CD4 count as an outcome

Paths	***β***	***SE***	***p-value***
IS ---» ARTS	-0.105	0.030	**<0.001**
AS ---» ARTS	-0.134	0.028	**<0.001**
ES ---» ARTS	-0.211	0.042	**<0.001**
IS ---» ARTM	-0.028	0.009	**0.003**
AS ---» ARTM	-0.064	0.009	**<0.001**
ES ---» ARTM†	0.023	0.014	0.095
IS ---» MED†	0.005	0.012	0.701
AS ---» MED†	-0.006	0.013	0.646
ES ---» MED	-0.056	0.020	**0.006**
ARTS ---» MED	0.063	0.014	**<0.001**
ARTM ---» MED	0.104	0.041	**0.012**
IS ---» CD4 count†	0.016	0.019	0.376
AS ---» CD4 count†	-0.023	0.018	0.213
ES ---» CD4 count†	0.048	0.031	0.118
ARTS ---» CD4 count†	0.015	0.019	0.425
ARTM ---» CD4 count†	-0.021	0.058	0.714
MED ---» CD4 count	-0.056	0.027	**0.040**

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; *SE*: Standard error; †: Insignificant paths were deleted in model trimming process.

Table C.2 Original path model with viral suppression as an outcome

Paths	***β***	***SE***	***p-value***
IS ---» ARTS	-0.105	0.026	**<0.001**
AS ---» ARTS	-0.134	0.028	**<0.001**
ES ---» ARTS	-0.211	0.041	**<0.001**
IS ---» ARTM	-0.028	0.008	**<0.001**
AS ---» ARTM	-0.064	0.008	**<0.001**
ES ---» ARTM†	0.023	0.012	0.063
IS ---» MED†	0.005	0.012	0.687
AS ---» MED†	-0.006	0.013	0.632
ES ---» MED	-0.056	0.018	**0.002**
ARTS ---» MED	0.063	0.013	**<0.001**
ARTM ---» MED	0.104	0.038	**0.006**
IS ---» VS†	-0.005	0.007	0.511
AS ---» VS†	-0.008	0.008	0.287
ES ---» VS†	0.012	0.011	0.273
ARTS ---» VS†	0.005	0.008	0.508
ARTM ---» VS†	0.013	0.023	0.570
MED ---» VS	-0.036	0.011	**0.001**

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; VS: Viral suppression; SE: Standard error; †: Insignificant paths were deleted in model trimming process.

Table C.3 Original path model with HRQoL as an outcome

Paths	***β***	***SE***	***p-value***
IS ---» ARTS	**-0.106**	**0.027**	**<0.001**
AS ---» ARTS	**-0.133**	**0.028**	**<0.001**
ES ---» ARTS	**-0.213**	**0.042**	**<0.001**
IS ---» ARTM	**-0.029**	**0.008**	**<0.001**
AS ---» ARTM	**-0.063**	**0.009**	**<0.001**
ES ---» ARTM†	0.023	0.013	0.066
IS ---» MED†	0.003	0.012	0.821
AS ---» MED†	-0.005	0.013	0.690
ES ---» MED	**-0.056**	**0.019**	**0.003**
ARTS ---» MED	**0.063**	**0.013**	**<0.001**
ARTM ---» MED	**0.120**	**0.039**	**0.002**
IS ---» HRQoL	**-0.186**	**0.040**	**<0.001**
AS ---» HRQoL†	-0.080	0.042	0.056
ES ---» HRQoL	**-0.309**	**0.061**	**<0.001**
ARTS ---» HRQoL	**0.374**	**0.042**	**<0.001**
ARTM ---» HRQoL	**0.977**	**0.131**	**<0.001**
MED ---» HRQoL†	0.064	0.058	0.271

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; HRQoL: Health-related quality of life; *SE*: Standard error; †: Insignificant paths were deleted in model trimming process.

APPENDIX D

MODIFICATION INDICES

Table D.1 Adjusted paths and modification indices in the final model with CD4 count as an outcome

Paths	***M.I.***	***E.P.C***	***StdYX E.P.C***
Internalized stigma (intercept) «---» Enacted stigma (intercept)	73.625	0.631	0.183
Anticipated stigma (intercept) «---» Enacted stigma (intercept)	72.268	0.864	0.208
Anticipated stigma (intercept) «---» Internalized stigma (intercept)	234.313	4.033	0.351
ART self-efficacy (intercept) «---» Enacted stigma (intercept)	27.724	-0.414	-0.130
ART self-efficacy (intercept) «---» Internalized stigma (intercept)	131.110	-2.228	-0.254
ART self-efficacy (intercept) «---» Anticipated stigma (intercept)	96.334	-2.746	-0.260
HIV symptom management self-efficacy (intercept) «---» Enacted stigma (intercept)	47.763	-0.814	-0.156
HIV symptom management self-efficacy (intercept) «---» Internalized stigma (intercept)	161.181	-3.700	-0.257
HIV symptom management self-efficacy (intercept) «---» Anticipated stigma (intercept)	134.812	-4.864	-0.281
HIV symptom management self-efficacy (intercept) «---» ART self-efficacy (intercept)	299.680	5.675	0.430
HIV symptom management self-efficacy (intercept) «---» CD4 (intercept)	27.551	1.642	0.073
ART adherence (intercept) «---» ART self-efficacy (intercept)	46.115	0.471	0.115
Age «---» Internalized stigma (intercept)	24.803	3.228	0.114
Age «---» HIV symptom management self-efficacy (intercept)	20.415	-4.934	-0.116
Age «---» CD4 count (intercept)	49.498	-9.535	-0.203
Age «---» HIV symptom management self-efficacy (slope)	13.576	-0.160	-0.102

Note: «---»: Correlation.

Table D.2 Adjusted paths and modification indices in the final model with viral suppression as an outcome

Paths	***M.I.***	***E.P.C***	***StdYX E.P.C***
Internalized stigma (intercept) «---» Enacted stigma (intercept)	73.625	0.631	0.183
Anticipated stigma (intercept) «---» Enacted stigma (intercept)	72.268	0.864	0.208
Anticipated stigma (intercept) «---» Internalized stigma (intercept)	234.314	4.033	0.351
ART self-efficacy (intercept) «---» Enacted stigma (intercept)	27.724	-0.414	-0.130
ART self-efficacy (intercept) «---» Internalized stigma (intercept)	131.110	-2.228	-0.254
ART self-efficacy (intercept) «---» Anticipated stigma (intercept)	96.334	-2.746	-0.260
HIV symptom management self-efficacy (intercept) «---» Enacted stigma (intercept)	47.763	-0.814	-0.156
HIV symptom management self-efficacy (intercept) «---» Internalized stigma (intercept)	161.181	-3.700	-0.257
HIV symptom management self-efficacy (intercept) «---» Anticipated stigma (intercept)	134.812	-4.864	-0.281
HIV symptom management self-efficacy (intercept) «---» ART self-efficacy (intercept)	299.680	5.675	0.430
ART adherence (intercept) «---» ART self-efficacy (intercept)	46.115	0.471	0.115
Duration of infection «---» ART self-efficacy (intercept)	25.634	-9.603	-0.142
Depression «---» ART self-efficacy (intercept)	36.162	-5.499	-0.168
Depression «---» HIV symptom management self-efficacy (intercept)	20.404	-6.186	-0.116
Depression «---» ART self-efficacy (slope)	11.855	0.586	0.099

Note: «---»: Correlation.

Table D.3 Adjusted paths and modification indices in the final model with HRQoL as an outcome

Paths	***M.I.***	***E.P.C***	***StdYX E.P.C***
Internalized stigma (intercept) «---» Enacted stigma (intercept)	73.126	0.630	0.184
Anticipated stigma (intercept) «---» Enacted stigma (intercept)	70.822	0.861	0.208
Anticipated stigma (intercept) «---» Internalized stigma (intercept)	224.261	3.932	0.347
ART self-efficacy (intercept) «---» Enacted stigma (intercept)	32.002	-0.445	-0.142
ART self-efficacy (intercept) «---» Internalized stigma (intercept)	127.472	-2.182	-0.253
ART self-efficacy (intercept) «---» Anticipated stigma (intercept)	93.166	-2.695	-0.259
HIV symptom management self-efficacy (intercept) «---» Enacted stigma (intercept)	44.665	-0.793	-0.153
HIV symptom management self-efficacy (intercept) «---» Internalized stigma (intercept)	160.770	-3.692	-0.259
HIV symptom management self-efficacy (intercept) «---» Anticipated stigma (intercept)	129.133	-4.780	-0.279
HIV symptom management self-efficacy (intercept) «---» ART self-efficacy (intercept)	294.952	5.630	0.431
ART adherence (intercept) «---» ART self-efficacy (intercept)	46.716	0.470	0.116
HRQoL (intercept) «---» Enacted stigma (intercept)	117.539	-2.524	-0.278
HRQoL (intercept) «---» Internalized stigma (intercept)	180.932	-7.678	-0.309
HRQoL (intercept) «---» Anticipated stigma (intercept)	165.358	-10.605	-0.353
HRQoL (intercept) «---» ART self-efficacy (intercept)	281.787	10.789	0.473
HRQoL (intercept) «---» HIV symptom management self-efficacy (intercept)	271.441	15.955	0.424
Depression «---» Enacted stigma (intercept)	13.551	0.380	0.076
Depression «---» Internalized stigma (intercept)	22.219	1.235	0.091
Depression «---» Anticipated stigma (intercept)	24.140	1.620	0.094
Depression «---» ART self-efficacy (intercept)	21.149	-1.446	-0.113
Depression «---» HIV symptom management self-efficacy (intercept)	25.208	-1.944	-0.090
Depression «---» HRQoL (Intercept)	39.347	-4.788	-0.127
Anxiety «---» Enacted stigma (intercept)	47.065	1.261	0.181
Anxiety «---» Internalized stigma (intercept)	51.010	3.197	0.171

Anxiety «---» Anticipated stigma (intercept)	38.316	3.882	0.168
Anxiety «---» ART self-efficacy (intercept)	20.793	-1.601	-0.089
Anxiety «---» HIV symptom management self-efficacy (intercept)	36.581	-3.769	-0.140
Anxiety «---» HRQoL (intercept)	117.803	-11.319	-0.219
CD4 count «---» ART self-efficacy (intercept)	12.091	0.120	0.086
CD4 count «---» HIV symptom management self-efficacy (intercept)	28.874	0.318	0.138
Duration of infection «---» CD4 count	19.360	0.195	0.125

Note: «---»: Correlation.

APPENDIX E

SUBGROUP ANALYSIS OF VIRAL SUPPRESSION

Table E.1 Path coefficients of mediation analysis by baseline CD4 count

Paths	***β***	***Std.β***	***SE***	***p-value***
Group: CD4 count < 500 cells/µl (*n*= 658)				
Internalized stigma ---» ART self-efficacy	-0.124	-0.142	0.039	**0.001****
Anticipated stigma ---» ART self-efficacy	-0.113	-0.122	0.036	**0.002****
Enacted stigma ---» ART self-efficacy	-0.133	-0.097	0.054	**0.014***
Internalized stigma ---» HIV symptom management self-efficacy	-0.008	-0.025	0.013	0.562
Anticipated stigma ---» HIV symptom management self-efficacy	-0.068	-0.211	0.013	**<0.001*****
Enacted stigma ---» ART adherence	-0.040	-0.041	0.027	0.144
ART self-efficacy ---» ART adherence	0.083	0.117	0.019	**<0.001*****
HIV symptom management self-efficacy ---» ART adherence	0.049	0.024	0.056	0.384
ART adherence ---» Viral suppression	-0.027	-0.023	0.016	0.102
Group: CD4 count ≥ 500 cells/µl (*n*= 540)				
Internalized stigma ---» ART self-efficacy	-0.096	-0.103	0.045	**0.032***
Anticipated stigma ---» ART self-efficacy	-0.142	-0.146	0.042	**0.001****
Enacted stigma ---» ART self-efficacy	-0.297	-0.183	0.069	**<0.001*****
Internalized stigma ---» HIV symptom management self-efficacy	-0.016	-0.057	0.013	0.209
Anticipated stigma ---» HIV symptom management self-efficacy	-0.052	-0.176	0.014	**<0.001*****

Enacted stigma ---» ART adherence	-0.080	-0.073	0.032	**0.011***
ART self-efficacy ---» ART adherence	0.045	0.066	0.019	**0.017***
HIV symptom management self-efficacy ---» ART adherence	0.123	0.056	0.054	**0.022***
ART adherence ---» Viral suppression	-0.045	-0.048	0.017	**0.008****

Note: *CI*: Confidence interval; *SE*: Standard error; *: p<0.05; **: p<0.01; ***: p<0.001.

Table E.2 Results of longitudinal mediation analysis of viral suppression by baseline CD4 count

Effects	***β***	***Std.β***	***SE***	***p-value***
Group: CD4 count < 500 cells/μl (*n*= 658)				
From IS to VS				
Indirect effect				
IS ---» ARTS ---» MED ---» VS	0.000	0.000	0.000	0.174
IS ---» ARTM ---» MED ---» VS	0.000	0.000	0.000	0.779
From AS to VS				
Indirect effect				
AS ---» ARTS ---» MED ---» VS	0.000	0.000	0.000	0.183
AS ---» ARTM ---» MED ---» VS	0.000	0.000	0.000	0.501
From ES to VS				
Indirect effect				
ES ---» MED ---» VS	0.001	0.001	0.001	0.319
ES ---» ARTS ---» MED ---» VS	0.000	0.000	0.000	0.258
From IS to MED				
Indirect effect				
IS ---» ARTS ---» MED	-0.011	-0.017	0.004	**0.009****
IS ---» ARTM ---» MED	0.000	-0.001	0.001	0.740
From AS to MED				
Indirect effect				
AS ---» ARTS ---» MED	-0.009	-0.014	0.004	**0.012***
AS ---» ARTM ---» MED	-0.003	-0.005	0.004	0.398
From ES to MED				
Indirect effect				
ES ---» ARTS ---» MED	-0.011	-0.011	0.005	**0.034***
Direct effect	-0.040	-0.041	0.027	0.144

Group: CD4 count ≥ 500 cells/µl (*n*= 540)				
From IS to VS				
Indirect effect				
IS ---» ARTS ---» MED ---» VS	0.000	0.000	0.000	0.227
IS ---» ARTM ---» MED ---» VS	0.000	0.000	0.000	0.320
From AS to VS				
Indirect effect				
AS ---» ARTS ---» MED ---» VS	0.000	0.000	0.000	0.113
AS ---» ARTM ---» MED ---» VS	0.000	0.000	0.000	0.119
From ES to VS				
Indirect effect				
ES ---» MED ---» VS	0.004	0.003	0.002	0.072
ES ---» ARTS ---» MED ---» VS	0.001	0.001	0.000	0.132
From IS to MED				
Indirect effect				
IS ---» ARTS ---» MED	-0.004	-0.007	0.003	0.150
IS ---» ARTM ---» MED	-0.002	-0.003	0.002	0.292
From AS to MED				
Indirect effect				
AS ---» ARTS ---» MED	-0.006	-0.010	0.003	**0.039****
AS ---» ARTM ---» MED	-0.006	-0.010	0.004	0.067
From ES to MED				
Indirect effect				
ES ---» ARTS ---» MED	-0.013	-0.012	0.007	**0.044***
Direct effect	-0.080	-0.073	0.032	**0.011***

Note: IS: Internalized stigma; AS: Anticipated stigma; ES: Enacted stigma; ARTS: ART self-efficacy; ARTM: HIV symptom management self-efficacy; MED: ART adherence; VS: Viral suppression; *CI*: Confidence interval; *SE*: Standard error; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.