

ASSESSING THE EFFECTS OF A NOVEL INTERVENTION FOR ANTIRETROVIRAL
MEDICATION ADHERENCE

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by
Sofie Ling Champassak

B.A., San Diego State University, 2010
M.A., University of Missouri-Kansas City, 2012

Kansas City, Missouri
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Sofie Ling Champassak, Candidate for the Doctor of Philosophy Degree

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ABSTRACT

The use of antiretroviral therapy (ART) has led to substantial declines in morbidity and mortality in patients with HIV, however the benefits of ART are largely dependent on strict adherence. Effective interventions have been developed to improve adherence that include the use of cognitive behavioral treatment techniques or external supports such as modified directly observed therapy (mDOT). Project MOTIV8 assessed whether a novel intervention combining motivational interviewing based cognitive behavioral therapy (MI-CBT) counseling with modified directly observed therapy (mDOT) was more effective than MI-CBT counseling alone or standard care (SC) for increasing ART adherence (Goggin et al., 2013). The results demonstrated an interaction effect such that the combined MI-CBT/mDOT group had its greatest effect at week 12 of the intervention, and then adherence rates declined more rapidly than the SC and MI-CBT groups as the intervention concluded. The aim of this study was to enhance our understanding of the intervention effects found in Project MOTIV8 by identifying how mediator variables were impacted by treatment throughout the course of the study. Treatment was based primarily on the Information-Motivation-Behavioral Skills Model and included variables that measured participants'

adherence information (knowledge about ART), adherence motivation (personal and perceptions of significant others' attitudes and beliefs that impact patients' motivation), and adherence behavioral skills (e.g., acquiring medications and social support for adherence). Data for this secondary data analysis comes from Project MOTIV8 and was collected at baseline, week 24, and week 48. Participants were recruited from six outpatient clinics and stratified by ART experience and clinic. Data from 204 participants were available for analysis. Participants were on average 40 years old, 76% were male, and 57% were African American. A total of 14 mediator variables were measured throughout the course of the intervention. A principal components analysis (PCA) was used to reduce the number of variables and structural equation modeling (SEM) was used to determine which mediator variables were impacted by treatment and which mediator variables predicted adherence. The results of the PCA identified three latent IMB constructs which included 11 of the 14 mediator variables. The results of a SEM analysis revealed that mDOT significantly decreased participants' adherence information and increased adherence motivation at the end of treatment. However these effects weren't found during the 6-month follow-up. There were no significant effects found between MI-CBT and any of the IMB constructs. Only adherence motivation had a significant positive effect on adherence at the 6-month follow-up. These findings provide direction for improving treatment and advancing treatment research.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the College of Arts and Sciences have examined a dissertation titled “Assessing the Effects of a Novel Intervention for Antiretroviral Medication Adherence,” presented by Sofie Ling Champassak, candidate for the Doctor of Philosophy degree, and hereby certify that in their opinion it is worthy of acceptance.

Supervisory Committee

Delwyn Catley, Ph.D., Committee Chair
Department of Psychology

Jannette Berkley-Patton, Ph.D.
Department of Psychology

Jared Bruce, Ph.D.
Department of Psychology

Kathy Goggin, Ph.D.
Health Services and Outcomes Research
Children’s Mercy Hospitals and Clinics

Amanda Bruce, Ph.D.
Department of Pediatrics
University of Kansas Medical Center

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CHAPTER 1

INTRODUCTION

The use of antiretroviral therapy (ART) has been shown to suppress viral load, increase rates of survival and improve quality of life in patients with HIV. High levels of adherence ($\geq 90\%$) are required for these benefits and are challenging and often not sustained over time. Average rates of ART adherence have been found to be between 50 and 70% (Krummenacher, Cavassini, Bugnon, & Schneider, 2011). Many factors contribute to low levels of adherence including individual factors (e.g., knowledge, motivation), factors related to the medications (e.g., side-effects, perceived difficulty of regimen), and environmental factors (e.g., access to care, adherence support).

To address these barriers, effective interventions have targeted various factors to increase rates of adherence. Previous studies have tested the effect of comprehensive ART adherence using counseling interventions that include motivational interviewing (MI) and cognitive behavioral treatment (CBT) techniques while other studies have included external supports such as modified directly observed therapy (mDOT). These approaches have demonstrated some promise in improving ART adherence (Altice, Maru, Bruce, Springer, and Friedland, 2007; Amico, Harman, & Johnson, 2006; Golin, Earp, Tien, Stewart, Porter, & Howie, 2006; Hart, Jeon, Ivers, Behforouz, Caldas, Drobac, & Shin, 2010).

To date, only one study, Project MOTIV8, has examined the combined effect of motivational interviewing-based cognitive behavioral therapy (MI-CBT) counseling with mDOT approaches (Goggin, Gerkovich, Williams, Banderas, Catley, Berkley-Patton, Wagner, Stanford, Neville, Kumar, Bamberger, & Clough, 2013). This study assessed the efficacy of MI-CBT counseling combined with mDOT compared to MI-CBT counseling alone or standard care (SC)

to impact ART adherence. Findings included a significant interaction of group by time, but no main effect of group. Post hoc analyses of the significant interaction revealed only trends for differences between groups at week 12. Specifically the combined MI-CBT/mDOT intervention group had the highest average adherence at week 12, and then saw a steady decline to rates below the SC and MI-CBT groups as the study concluded.

There are at least a couple of reasons why efficacy studies fail to demonstrate significant main effects. Either the interventions were ineffective in impacting the theoretical mediators of the outcome or the theoretical mediators had no impact on the outcome. Evaluating theoretical mediators is of vital importance for increasing understanding of theoretical mediators and improving the efficiency and effectiveness of interventions (Glasgow, 2002). Unfortunately, despite the significant number of ART adherence trials, there is a lack of published research in which the role of mediators is explored (Leeman, Chang, Voils, Crandell, & Sandelowski, 2011).

Theoretical Perspective

This study's interventions were based on the Information-Motivation-Behavioral Skills (IMB) model of behavior change, (Fisher & Fisher, 1992; Fisher, Fisher, Misovich, Kimble, & Malloy, 1996) which suggests that information is a prerequisite to modify behavior but is not sufficient alone. According to this model, critical components to promote behavior change also include a person's motivation and behavioral skills. Information and motivation work together through behavior skills to affect behavior, although information and motivation can also independently directly influence behavior (Figure 1). The IMB model has been applied to the development of adherence interventions to demonstrate effective behavior change across a variety of clinical applications including HIV medication adherence and self-care behaviors in adults with type 2 diabetes (Carey, Maisto, Kalichman, Forsyth, Wright, & Johnson, 1997;

Fisher & Fisher, 1992; Fisher, Fisher, Misovich, Kimble, & Malloy, 1996; Gao, Wang, Zhu, & Yu, 2013; Mayberry & Osborn, 2014; Gavvani, Poursharifi, & Aliasgarzadeh, 2010; Rongkavilit et al., 2010; Walsh, Senn, Scott-Sheldon, Vanable, & Carey, 2011).

The goal of the motivational interviewing (MI) intervention components in this study was primarily to enhance motivation while the cognitive-behavioral aspects of the intervention were intended primarily to enhance knowledge and skills (including self-efficacy) for adherence. The theoretical underpinnings of mDOT are unclear, however it was assumed that mDOT would ultimately foster adherence skills through repeated prompted practice.

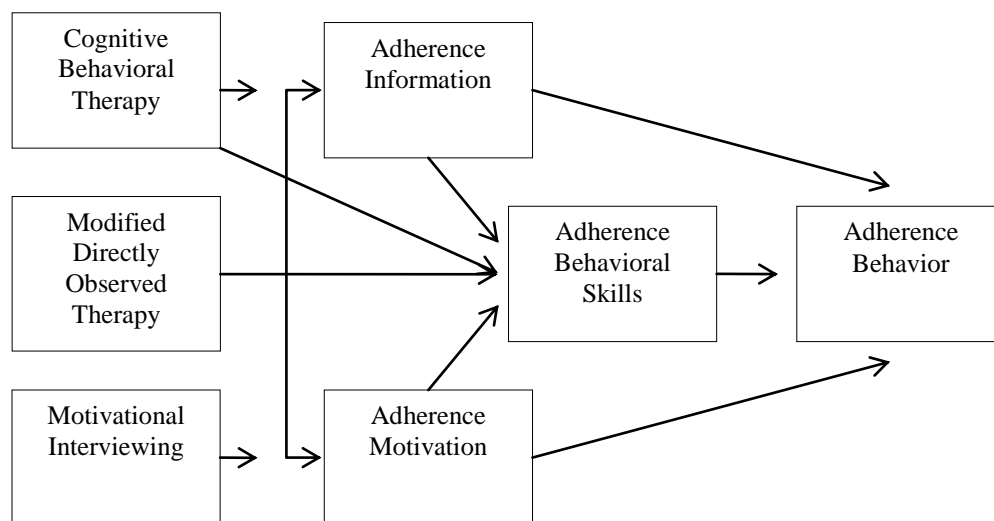


Figure 1. Information-Motivation-Behavioral Skills Model of Adherence

Based on these intervention goals a number of IMB based mediator variables were assessed. Information variables included knowledge about ART and medication adherence. Motivation variables included motivation, readiness and confidence to adhere, autonomous regulation, autonomy support, perceived costs and benefits of ART, and perceived social support for ART adherence. Because of the practical difficulty of assessing behavioral adherence skills, the study assessed adherence skills indirectly through measures of self-efficacy for adherence, perceived difficulty of adherence, and reasons for non-adherence (e.g., a variety of reasons

participants may have missed taking their medications related to the patient, medicine, or logistics).

The purpose of this study was to advance understanding of adherence intervention effects by exploring the role of IMB based mediator variables in Project MOTIV8. Specifically the study examined the impact of MI-CBT/mDOT relative to MI-CBT and standard care on IMB based mediator variables as well as the relationship between changes in mediator variables and adherence.

CHAPTER 2 BACKGROUND

Antiretroviral Therapy (ART) and ART Adherence

Antiretroviral therapy (ART) is a combination of at least three antiretroviral (ARV) drugs to suppress and stop the human immunodeficiency virus (HIV) from reaching the most advanced stage of infection known as acquired immunodeficiency syndrome (AIDS; WHO, 2014).

Adhering to ART can lower the amount of viral load in the body to improve health and prolong life in people living with HIV/AIDS (CDC, 2013). Moreover, good adherence can reduce the risk of transmitting HIV to others by over 90% (Attia, Egger, Müller, Zwahlen, & Low, 2009; Cohen, Chen, McCauley, et al., 2011). However, high levels of adherence ($\geq 90\%$) are critical to achieve these individual and public health benefits (Chesney, 2006; WHO, 2003). Yet the average rates of ART adherence have been found to be between 50 and 70% (Chesney, Ickovics, Chambers, Gifford, Neidig, Zwickl, & Wu, 2000; Krummenacher et al., 2011). Missing doses can lead to HIV drug resistance (HIVDR) allowing the virus to mutate and reproduce in the presence of ARV drugs (Bangsberg, Moss, & Deeks, 2004). The consequences of HIVDR include treatment failure, increased health care costs associated with the need to start more expensive treatments, spreading drug resistant HIV, and the need to develop new anti-HIV drugs (WHO, 2014).

Factors that Contribute to ART Adherence

There are a variety of factors that contribute to ART adherence including individual, medication-related, and environmental factors. Individual factors such as knowledge of ART and treatment regime, neurocognitive impairment, low health literacy, motivation, self-efficacy, age, mental illness, and substance use have been shown to be associated with ART adherence (Carr & Gramling, 2004; Demessie, Mekonnen, Wondwossen, & Shibeshi, 2014; Halkitis,

Shrem, Zade, & Wilton, 2005; Safren et al., 2012; Safren et al., 2009). Factors related to taking ART medication such as number of pills, timing of doses (four, six, eight, or 12 hour intervals), side effects, food requirements (some should be taken on an empty stomach, with meals, fatty, or non-fatty foods), and dosing complexity have also been shown to be associated with ART adherence (Nachega et al., 2014; Raboud et al., 2011; Safren et al., 2001). Lastly, environmental factors such as adherence support, homelessness, access to care, characteristics of the clinical setting, and patient-provider relationship have also demonstrated a relationship with ART adherence (CDC 2012; Schneider, Kaplan, Greenfield, & Wilson, 2004; Thompson et al., 2012).

Effective Interventions to Increase ART Adherence

Cognitive Behavioral Therapy (CBT) Interventions

To improve adherence, effective interventions have targeted various factors to address individual, medication related, and environmental barriers. Interventions that have used counseling techniques such as cognitive behavioral therapy (CBT) have demonstrated some success in improving ART adherence (Chaiyachati et al., 2014). CBT is a form of psychotherapy that was developed to treat a variety of mental health disorders and has also been found to be effective for treating a variety of health conditions such as chronic pain, sleep disorders, and headaches. Over 300 research studies have been published that have evaluated the efficacy of CBT interventions for a wide range of psychiatric disorders and health conditions (Butler, Chapman, Forman, & Beck, 2006). Several of these studies test the efficacy of using CBT strategies to improve ART adherence. For example, a recent systematic review published by Chaiyachati et al. (2014) identified 60 intervention studies that utilized CBT techniques to improve ART adherence. Although the effects of CBT on ART adherence have been widely

assessed, the findings in the literature continue to be mixed. Moreover, significant effects tend to be small and diminish over time (Simoni, Amico, Smith, & Nelson, 2010).

For example, several researchers began using CBT in their interventions to focus on participants' individual barriers to adherence. Interventions have included CBT components such as providing advice and education, teaching stress management and coping skills using single or multiple sessions in one-on-one or via group settings (Goujard et al., 2003; Jones et al., 2007; Knobel et al., 1999; Murphy, Lu, Martin, Hoffman, & Marelich, 2002; Rawlings et al., 2003; Tuldra et al., 2000). Weber et al. (2004) conducted a one-year trial to examine the effect of CBT on ART adherence in 60 individuals with HIV. Participants were randomized to receive CBT or standard of care (SOC). Those in the CBT condition received individual counseling sessions from a psychotherapist and session content focused on participants' life goals. At least one goal was required to be related to ART adherence. Each month, adherence data was collected via self-report and downloaded from a medication event monitoring system (MEMS). The results demonstrated a significant difference in adherence during months 10-12 of the study between the CBT and SOC conditions such that those in the CBT condition had higher adherence than those in the SOC condition. Moreover, participants with adherence $\geq 95\%$ was 70% for the CBT condition and 50% for the SOC condition.

A more recent study integrated computer technology and CBT techniques to evaluate the efficacy of a computer based intervention (Fisher et al., 2011). The study took place during routinely scheduled visits in HIV care clinics over 18 months. Participants were 594 adults with HIV, randomized to an experimental condition which required participation in an interactive computer-based ART adherence promotion program or standard of care (SOC). Those in the experimental condition received adherence promotion strategies, selected and engaged in an

activity (20 different CBT modules), and chose an adherence related goal. Subsequent sessions included an update on the progress of previous goals, completing additional intervention activities, and selecting additional adherence related goals. Adherence was measured using the AIDS Clinical Trials Group (ACTG) 3-day recall measure of doses taken (Chesney, Ickovics, Chambers et al., 2000) and a Visual Analogue Scale (VAS) adherence assessment (Walsh, Mandalia, & Gazzard, 2002). Adherence was defined as a dichotomous variable (100% vs. imperfect adherence). Results indicated that participants who regularly used the computer-based intervention achieved significantly higher levels of adherence. This effect was observed over 14 visits while adherence decreased for participants in the SOC condition.

Similar results have been found in additional studies that have evaluated the use of CBT to improve ART Adherence (Knobel et al., 1999; Lyon et al., 2003; Margolin et al., 2003; Ramirez-Garcia & Cote, 2012; Weiss et al., 2011). However not all studies have demonstrated successful results (Antoni et al., 2006; Duncan et al., 2012; Funck-Brentano et al., 2005; Holzemer et al., 2006; Murphy et al., 2007; Tuldra et al., 2000; Wamalwa et al., 2009). The discrepant findings raise concerns about whether CBT alone is sufficient to improve ART adherence.

CBT and Motivational Interviewing (MI) Interventions

Interventions using CBT techniques in conjunction with motivational interviewing (MI) have shown to positively impact adherence. MI is a person-centered counseling style designed to strengthen motivation and commitment to change by eliciting and exploring an individual's own reasons for change in an environment that include acceptance and compassion (Miller, 2012). This counseling style was originally created for use with individuals with substance use disorders and has been used with a variety of populations and behaviors including mental health

disorders and health-promotion behaviors in over 200 randomized trials (Miller & Rose, 2009). MI has been applied to ART adherence interventions through patient-centered counseling techniques which include eliciting participants' adherence-related concerns, use of reflective listening during discussions about participants' ideas, feelings, and ambivalence about adherence, discussions about importance and confidence to adhere, and providing ideas (with permission) to help change adherence-related behavior (Golin et al., 2006).

Studies have found that MI in conjunction with CBT techniques have been effective to produce comprehensive ART adherence interventions to assist people living with HIV overcome difficulties with adherence (Ingersoll et al., 2011; Parsons, Golub, Rosof, & Holder, 2007; Safren et al., 2001). Safren et al. (2001) evaluated the efficacy of an intervention that utilized MI, CBT, and problem solving therapy techniques in a randomized controlled trial consisting of 56 adults with HIV across 12 weeks. Adherence was measured using an adherence questionnaire that asked participants about adherence during the past two weeks and was obtained from the participants' daily pill diary. Participants were randomized to a self-monitoring or life-steps condition. Those in the self-monitoring condition were required to utilize a daily diary to record adherence. Those in the life-steps condition participated in a single session that incorporated 11 informational, motivational, problem-solving, and cognitive behavioral steps. Results indicated improved adherence for both conditions with higher percentages of adherence for those in the life-steps condition.

Similarly, Parsons, Golub, Rosof, and Holder (2007) evaluated the efficacy of an intervention that combined MI and CBT techniques to improve ART adherence. Participants included 143 adults with HIV who also met criteria for hazardous drinking (>16 drinks per week for men or >12 drinks per week for women). Participants were randomized to receive eight MI-

CBT sessions or a time and content equivalent educational condition. Adherence was measured via self-report asking participants to recall all medication doses taken and missed in the previous two weeks. Drinking behavior was assessed in a similar manner by asking participants the total number of consumed drinks in the previous two weeks. Data was collected at baseline, three, and six-month follow-up. Results indicated that participants in both conditions reported significant increases in percent dose and percent day adherence between baseline and three months. Additionally, participants who received the MI-CBT sessions had significantly greater improvement in adherence for percentage of doses and daily adherence compared to those in the education condition. Improvements in adherence were maintained for both groups at six months and those in the intervention continued to report better adherence compared to the education only condition, although this difference was no longer statistically significant. There were no significant differences found between conditions for alcohol use.

Directly Observed Therapy

Interventions aimed at improving adherence have also used external supports such as directly observed therapy (DOT) which require supervision during each ingested dose of a medication regime. DOT has shown to be effective in improving adherence to tuberculosis (TB) therapy (Chaisson et al., 2001; Chaulk & Kazandjian, 1998; Chaulk & Iseman, 1997; Frieden, Fujiwara, Washko, & Hamburg, 1995; Curtis, Friedman, Neaigus, Jose, Goldstein, & Jarlais, 1994) and improving ART adherence in naïve patients in controlled settings (Altice, Maru, Bruce, Springer, & Friedland, 2007; Babudieri, Aceti, D'Offizi, Carbonara, & Starnini, 2000; Fischl, Rodriguez, Scerpella, Monroig, Thompson, & Rechtine, 2000; Fontanarosa, Babudieri, Aceti, D'Offizi, Carbonara, & Starnini, 2000). Fischl et al. (2000) examined prisoners enrolled in clinical trials who were receiving DOT or self-administered ART. Although those receiving

DOT had higher viral loads and lower CD4 counts at baseline, after 48 weeks of therapy more patients receiving DOT had lower viral load than patients who were self-administering ART. Similarly, Fontanarosa et al. (2000) compared prisoners who received DOT to self-administered ART and found comparable results. All patients who received DOT had a significant decrease in viral load after therapy, and 62% had a viral load below the detection limit compared to 34% of patients who self-administered ART. Meta-analyses that have assessed the effect of DOT on ART adherence have revealed contradictory results. Ford, Nachega, Engel, & Mills (2009) conducted a systematic review and meta-analysis of RCTs comparing DOT and self-administered ART. Virologic suppression at the study completion was used as the primary outcome measure. They reviewed ten studies and concluded that DOT did not offer any benefit over self-administered treatment. However, Hart et al. (2010) conducted a similar review and found differing results. Adherence, virologic and immunologic response were used as outcome measures. A review of 17 studies concluded that recipients of DOT were more likely to achieve an undetectable viral load, had greater increases in CD4 cell counts, and had ART adherence $\geq 95\%$ compared to recipients who self-administered ART.

The use of DOT has demonstrated some promise in improving adherence and health outcomes, however cost and feasibility need to be considered. Treatment for HIV is life long and can include multiple doses that need to be ingested at different times of the day. An alternative to DOT called observed therapy (OT) or modified DOT (mDOT) was created as a solution to the issue of observing each dose. This approach requires the supervision of ingesting a portion of the total doses and has been shown to be effective in a sample of patients with a history of adherence difficulties, incarceration, and active substance use disorder (Mitty, McKenzie, Stenzel, Flanigan, & Carpenter, 1999; Stenzel, McKenzie, Adelson-Mitty, &

Flanigan, 2000; Stenzel, McKenzie, Mitty, & Flanigan, 2001; Senak, 1997). Mitty, McKenzie, Stenzel, Flanigan, and Carpenter (1999) evaluated the use of a community based mDOT for participants who were referred by their primary care physician because of ART nonadherence and/or active substance use. Medication was initially delivered 5-7 days a week and then tapered to 1-3 days per week after three months. Data was collected at baseline, one, three, and six months. Results demonstrated a decrease in viral load and an increase in CD4 cell count for those who received mDOT at three and six months. Lucas et al. (2006) found similar results for participants who received care in methadone clinics. Participants received supervised doses of their ART regime on the mornings they received methadone at the clinic. Three different groups of participants were compared: patients with a history of injection drug use (IDU) who received methadone at the time ART was used (mDOT group), patients with a history of IDU who did not receive methadone at the time that ART was used (the IDU-nonmethadone group), and patients with no history of IDU (the non-IDU group). As found by Mitty et al. (1999), those who received mDOT had greater decreases in viral load and increases in CD4 cell counts compared to the two other groups. These results suggest that mDOT has the potential to provide benefits for people living with HIV/AIDS (Goggin, Liston, & Mitty, 2007).

The combination of MI and CBT techniques has demonstrated some promise in improving ART adherence, however the studies discussed thus far have used self-report measures of adherence. This approach is simple and inexpensive to use, but has many disadvantages including recall bias (Gagné, 2005), social desirability (Farmer, 199), and over-estimating adherence (Miller & Hays, 2000; Turner, 2002). To overcome these disadvantages, researchers have used Medication Event Monitoring Systems (MEMS) in addition to self-report measures of adherence (DiIorio et al., 2008; Golin, Earp, Tien, Stewart, Porter, & Howie, 2006).

MEMS are programmed to track the date and time the pill container is opened and has been cited as an effective approach to measure medication intake (Claxton, Cramer, & Pierce, 2001; de Bruin, Hospers, van den Borne, Kok, & Prins, 2005). Despite being more effective at measuring adherence than self-report, there are also biases found with this approach that may under or overestimate adherence due to “pocket dosing” (removing multiple pills at once for later use) or bottle-openings that aren’t followed by ingestion of medication (Bova, Fennie, Knafl, Dieckhaus, Watrous, & Williams, 2005). In summary, the combination of MI and CBT have been found to be effective for improving ART adherence, however the accuracy of measuring adherence using self-report and MEMS is an area of concern and additional approaches to measuring adherence should be evaluated.

Project MOTIV8: An Intervention that Combined MI-CBT and DOT

Project MOTIV8 was a novel intervention that assessed whether motivational interviewing-based cognitive behavioral therapy (MI-CBT) adherence counseling combined with modified directly observed therapy (MI-CBT/mDOT) was more effective than MI-CBT counseling alone or standard care (SC) in improving ART adherence and decreasing viral load. To date, this is the only intervention that has examined the combined effect of MI-CBT adherence counseling and mDOT. This randomized controlled trial took place over 48 weeks and adherence was monitored using an electronic drug monitor (EDM).

Project MOTIV8 Findings

Mixed regression models demonstrated significant interaction effects of the intervention over time on non-adherence (defined as percent of doses not-taken and not-taken on time) in the 30 days prior to each assessment. Post hoc ANOVA analyses revealed no significant group differences at each time point, but trends were found for better adherence at week 12 [$F(1,119) =$

3.67, $p = .058$] and poorer adherence at week 48 [$F(1, 110) = 3.21$, $p = .076$] for the MI-CBT/mDOT group compared to the SC group. The effect of group on viral load (undetectable compared to detectable) over time was examined using a logistic regression. The result revealed no significant relationship between group and undetectable viral load ($OR = .94$, 95% $CI = .67-1.32$, $p = .72$) and the odds of being undetectable significantly increased over time ($OR = 1.08$, 95% $CI = 1.07-1.10$, $p < .001$). The results of Project MOTIV8 demonstrated that the combined MI-CBT/mDOT intervention had its greatest impact during the most intensive component of the intervention (at week 12), and then indicated a steep decline as the treatment tapered and the study concluded (at week 24). These results suggest that the intervention did not have any impact on adherence. However, it is unclear why the intervention was ineffective. To explain why Project MOTIV8 failed to demonstrate significant main effects, an assessment of the theoretical mediators is required. It is important to evaluate whether the intervention was ineffective in impacting the theoretical mediators or the theoretical mediators were ineffective in impacting adherence.

Theoretical Mediators Targeted in Project MOTIV8

The interventions used in Project MOTIV8 were based on the Information-Motivation-Behavioral Skills (IMB) model of behavior change (Fisher & Fisher, 1992; Fisher, Fisher, Misovich, Kimble, & Malloy, 1996). This IMB model has been used to produce a comprehensive conceptualization of factors that impact ART adherence. The IMB model of highly active ART adherence was developed to facilitate effective intervention development (Fisher, Amico, Fisher, & Harman, 2008). According to this model (Figure 1), the main constructs of ART adherence include adherence-related information, motivation, and behavioral skills. Individuals who have more adherence information, motivation, and skills for completing

adherence related behavior will be more likely to adhere to their ART regime. Further, these main constructs work together to promote adherence behavior. For instance, an individual who has information about his or her regime, is motivated to adhere, and believes that his or

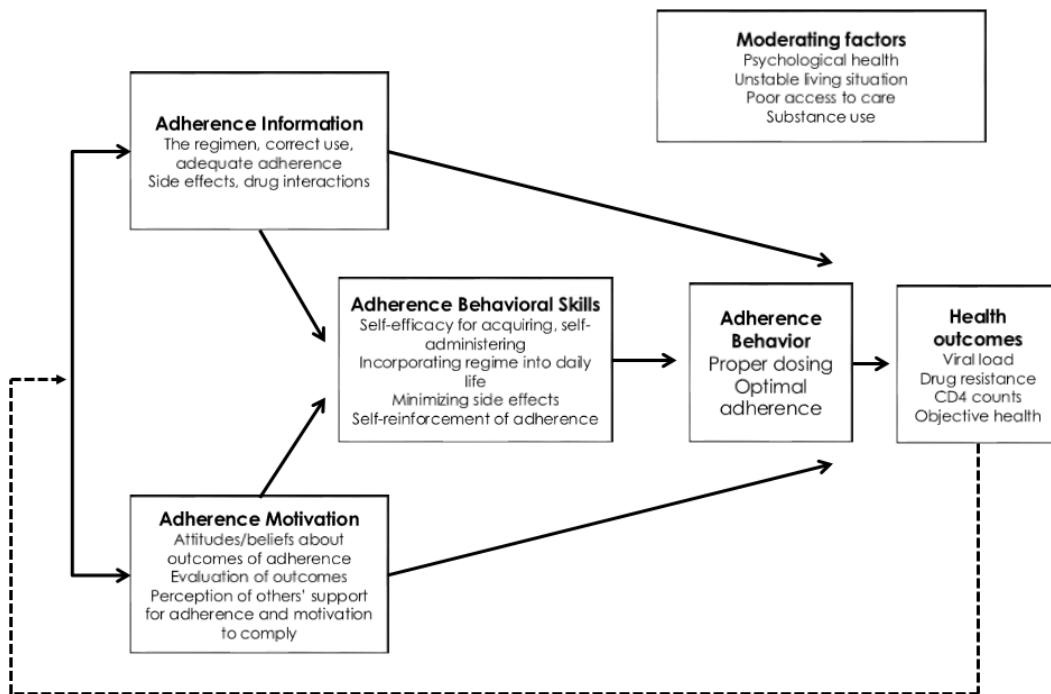


Figure 2. The Information-Motivation-Behavioral Skills model of antiretroviral therapy adherence information

her family support their adherence then he or she will engage in adherence related behavioral skills such as self-administering medications resulting in adherence behavior. Favorable health outcomes including increased CD4 cell counts and decreased viral load, are produced by the adherence behavior which is cycled back to influence subsequent levels of adherence information, motivation, and behavior skills in the future. Numerous interventions have been created using the IMB model of HAART adherence (Amico et al., 2009; Goggin et al., 2013;

Horvath, Smolenski, & Amico, 2014; Rongkavilit et al., 2010; Starace, Massa, Amico, & Fisher, 2006).

Project MOTIV8 targeted the components of the IMB model using CBT, MI, and mDOT. CBT techniques were used to target the information and behavioral skills components of the IMB model. MI was used to target the motivation component, and mDOT was used to target skills for adherence with the use of prompts and repeated practice. Knowledge, motivation, and skills for adherence were discussed in 10 counseling sessions. Although the intervention was developed to affect numerous IMB based mediating variables, the results suggested that either the MI-CBT and mDOT components of the intervention were ineffective at impacting the IMB based mediating variables or the mediating variables did not impact adherence. Much can be learned by exploring these possibilities in studies like MOTIV8 that fail to find main effects. Examining the mediators is critical to understanding why interventions do and do not work which contribute to the advancement of treatment and adherence treatment research (Kraemer et al., 2002). The present study examined the role of IMB based mediator variables in Project MOTIV8 by assessing the impact of MI-CBT/mDOT relative to MI-CBT and SC on IMB based mediator variables as well as the relationship between changes in mediator variables and adherence.

CHAPTER 3

METHODOLOGY

The data for this secondary analysis came from Project MOTIV8, a five year, three-armed, multi-site randomized controlled trial. The primary aim of this project was to assess whether motivational interviewing based cognitive behavioral therapy counseling with modified directly observed therapy (MI-CBT/mDOT) was more effective than motivational interviewing based cognitive behavioral therapy counseling alone (MI-CBT) or standard care (SC) for increasing ART adherence among 204 HIV-positive community clinic patients (Goggin et al., 2013).

Procedure

Data were collected at six outpatient clinics in Kansas City from December 2004 to August 2009. To be eligible to participate in the study, participants had to be HIV-positive and were starting ART for the first time, making a change in their regimen, or reported having adherence problems (which was confirmed by provider documentation). Eligible participants were also 18 years of age or older, spoke English and lived within a 70-mile radius of the project office. Participants were excluded if they did not self-administer their ART, were pregnant, or had an acute medical condition that would interfere with their participation in the study. All study procedures were approved by the appropriate Institutional Review Boards.

Participants completed baseline assessments that included demographic, adherence, and psychosocial variables using the Audio Computer Assisted Self Interview. Group randomization was stratified by clinic and ART naïve/experienced. Participants were given an electronic drug monitor (EDM; <http://www.aardex.ch>) to monitor adherence throughout the course of the study.

Data used for this analysis are from baseline, 24, and 48 weeks of the study, because data on mediator variables were collected at each of those time points.

Intervention

Motivational Interviewing Based Cognitive Behavioral Counseling (MI-CBT)

Participants assigned to the MI-CBT and MI-CBT/mDOT groups received care as usual from their clinic providers, six MI-CBT counseling sessions in person, and four telephone sessions with project staff members. The MI-CBT intervention included the use of MI techniques to increase motivation and confidence for change. Additionally, CBT approaches were used in an MI-consistent style to enhance knowledge and build skills for adherence during six face-to-face counseling sessions (weeks 0, 1, 2, 6, 11, and 23) and four telephone sessions (weeks 4, 9, 15, and 19). Counseling was conducted in 10 sessions and consisted of 11 different treatment modules (See Table 1). The first two sessions included enhancing motivation and confidence, and the self-monitoring modules, respectively. The patient was then given the opportunity to choose which module to discuss during the counseling session during the next seven sessions, and the last session included information on the relapse prevention module.

Modified Directly Observed Therapy (mDOT)

Participants in the MI-CBT/mDOT group received the same care as those in the MI-CBT group, but also received daily visits (Monday through Friday) from project staff to observe ingestion of an ART dose. For participants with multiple doses, only ingestion of one dose was observed. Each visit took place at a location and time that was most convenient for the participant. Daily visits occurred between baseline and week 16 of the study and were tapered between weeks 17 through 24, and ceased at week 24. Changes in medication regimes prescribed, late night dosing, and the inclusion of participants who lived outside the catchment

area led to revision of the mDOT protocol over the course of the study to include in person as well as ‘phone contacts’ (participant ingested medication during a study staff initiated phone call at the predetermined dose time), ‘med delivery’ (medications delivered outside of target dosing time and participant reported by phone/text when ingested), and PDA visits (medications delivered outside of target dosing time and participant retrospectively reported on all unobserved doses using personal digital assistant).

Therapists and Fidelity

Counselors were Master’s degree level professionals, were trained in MI and supervised by a licensed clinical psychologist. All sessions were digitally recorded and received ongoing weekly supervision. To determine fidelity throughout the study, session tapes were randomly selected during supervision and coded using a 26-item coding scheme adapted from a prior study (Harris, Catley, Good, et al., 2010). Counselors achieved high fidelity throughout the course of the study with an average rating of 6.2 ($SD = 1$) on an overall summary item (“*Overall, how well did the counselor conduct this session?*”) scored on a 7-point scale ranging from poor to excellent (1-7).

Table 1. *Project MOTIV8 Counseling Treatment Modules*

Session 1	Enhancing motivation and confidence – Assess importance and confidence to adhere, discuss the positives and negatives of adherence, discuss the relationship between values and health
2	Self-monitoring – Discuss factors that facilitate and hinder patient's adherence
Patient Chooses	Goal setting – Review values and discuss relationship between adherence and values, elicit patient's reasons for taking medications, complete goal setting worksheet for treatment (patient creates a specific, realistic goal to complete for the week and determines methods to achieve goal)
Session 3-9	Problem solving – Discuss barriers to adherence and possible solutions to barriers; with permission, counselor suggests other solutions to barriers; patient determines best solution and actions to carry out solution
	Adherence aids and stimulus control – Engage patient in brainstorming ways to remind him/herself to take medications; determine which strategy is most helpful and discuss past examples of success; with permission, counselor suggests other strategies and tools that could be helpful in prompting to take medications on time
	Thought stopping – Counselor discusses specific strategy to counter negative thoughts (e.g., thoughts about undesirable side-effects of medications, pessimism about future of one's health) about taking medications
	Personal support – Patient identifies people in their lives who can be a source of support in treatment and how they could be helpful; with permission, discuss the difficulty of discussing HIV treatment with others
	Symptom management – Discuss symptoms and side-effects of medications; introduce symptom management skills (discussing with doctor, discuss factors that may decrease or increase symptoms, elicit other ideas from patient to try)
	Medication refill skills – Discuss steps to ensure medications are available; with permission, provide suggestions to have medications available
	Talking to your doctor – Explore previous communication with doctor; review pro and cons of discussing important topics with doctor; elicit other treatment concerns patient can discuss with their doctor; with permission, role-play the doctor interaction with the patient
Session 10	Relapse prevention – Discuss current and future barriers to adherence; elicit strategies for dealing with obstacles; discuss patient's experience and progress in the program; review strategies that have been most helpful in adhering to treatment

Measures

Baseline Measures

Demographic measures included age, race, gender, sexual orientation, education, income, housing status, relationship status, and number of children. Data were collected on alcohol and drug use, depression, and perceived stress. Clinically related baseline measures included CD4 cell count (< 200), viral load copies ($> 100,000$), having a protease inhibitor-based regimen, and starting ART for the first time. Study staff abstracted these data from participants' medical records.

Mediator Variables

Mediator variables included 14 observed variables that contributed to the three (IMB) constructs. The observed variables are listed under their hypothesized constructs below. Information related variables were measured using two different questionnaires.

Knowledge About ART

The first measure was a 12-item inventory of true/false/don't know items, developed to assess patients' knowledge of combination therapy, the concept of drug resistance, and the consequences of non-adherence (Wagner, Kanouse, Koegel, & Sullivan, 2004). Higher scores indicate higher levels of ART knowledge.

ART Medical Knowledge

A second scale was developed by project staff to provide a measure of the participant's knowledge of adherence to their ART medications. There is one general question that was answered by all participants: *How perfectly do you think you need to stick to your medication schedule for you to minimize the chance of developing resistance to your HIV medications? Please give your answer as a number between 0 and 100 where 0 means that you do not need to*

stick to your schedule at all (for instance, you can skip all doses or never take any doses on time), and 100 means that you need to stick perfectly to your schedule (for instance, you take all doses on time). The remaining questions asked participants about timing and time windows for their medication schedules. Higher percentage correct signifies greater levels of ART medication adherence knowledge.

Motivation related variables were measured using five different scales.

Motivation to Adhere

A 5-item self-report scale was developed for the project to assess participant's level of readiness to adhere. Items tapped "desire", "reasons", "need", and "commitment" to adhere and were developed based on the motivational constructs defined by Amrhein, Miller, Yahne, Palmer, and Fulcher (2003) and were rated on a scale from 0 (not ready at all) to 10 (absolutely ready). Higher scores indicate greater levels of motivation to adhere.

Autonomous and Controlled Motivation

The Treatment Self-Regulation Questionnaire (TSRQ) was used to measure autonomous motivation. Based on the Self-determination theory, this 12-item scale measured the extent to which participants engaged in specific health behaviors of their own volition because such behaviors held personal importance for them, rather than doing so as a response to external pressures. Two different subscales are included in this measure: autonomous motivation and controlled motivation. Items were modified to address ART adherence and were rated on a scale from 1 (strongly disagree) to 7 (strongly agree). Higher scores reflect greater levels of adherence because of autonomy or control from external pressures. An example for an autonomy item is: *The reason I would take my HIV medications as they were prescribed to me is because I feel that I want to take responsibility for my own health.* An example item for control is: *The reason I*

would take my HIV medications as they were prescribed to me is because I feel pressure from others to do so.

Autonomy Support From Providers

The Health Care Climate Questionnaire (HCCQ) was used to measure support for patient autonomy surrounding HIV medications from health care providers. The 6-item questionnaire based on principles of the Self-determination theory was modified for the purpose of this study to address adherence to HIV medications. Items were rated on a scale from 1 (strongly disagree) to 7 (strongly agree). Higher scores signify greater levels of support from providers. Example items include: *My health-care providers have provided me with choices and options about my HIV treatment (including not participating in treatment). My health-care providers understand how I see things with respect to my HIV treatment. My health-care providers convey confidence in my ability to participate in HIV treatment.*

Necessity and Concern for Adherence

Participants' beliefs about the personal benefits and costs of their ART regime were measured using a 10-item scale (Horne, Weinman, & Hankins, 1999). This measure includes two subscales: necessity and concern. Items were rated on a scale from 1 (strongly disagree) to 5 (strongly agree). Higher scores signify greater levels of necessity and concern for adherence. An example item from the necessity subscale is: *Without my medicines I would be very ill.* An example item from the concern subscale is: *Having to take medicines worries me.*

Social Support

Perceived social support for adherence was measured using a 4-item scale to assess participants' perceived social support for adherence in the last 30 days (Simoni, Frick, Lockhart,

& Liebovitz, 2002). Four items queried the number of people available from 0 (no one) to 3 (many). Higher scores signify greater amounts of social support for adherence.

Behavioral skill related variables were measured using three different measures.

Self-efficacy for Adherence

Participants' self-efficacy to adhere was measured using a 10-item self-report scale developed to assess level of confidence in performing specific medical management tasks (Chesney et al., 2000). Items were rated on a scale from 0 (cannot do at all) to 10 (certain I can do). Higher scores indicate greater levels of self-efficacy for adherence.

Patient, Logistical, and Medication Related Reasons for Nonadherence

Reasons for non-adherence were measured using an 18-item scale adapted from the Adult AIDS Clinical Trials Group (AACTG) measures (Chesney et al., 2000). The scale included a variety of reasons participants may have missed taking their medications and consisted of three different subscales: patient issues, logistics, and medication related. Items were rated on a scale from 0 (never) to 3 (often). Higher scores signified greater levels of non-adherence. Example items for patient, logistic, and medication issues include: *you were away from*, *you didn't have transportation to get a prescription or go to the pharmacy*, *you had too many pills to take* respectively.

Perceived Difficulty of Regime

Participants' difficulty of current medication regime was measured using a 7-item scale developed to assess perceived difficulty of regime when participants thought about number of pills, side effects of medications, and the overall difficulty (Kennedy, Goggin, & Nollen, 2004). Items were rated on a scale from 1 (not at all difficult) to 5 (extremely difficult). Higher scores signify greater perceived difficulty of medication regime.

Outcome Variable

Adherence

Antiretroviral therapy adherence ($\geq 90\%$) was measured using medication bottle caps that recorded the date and time of each opening. Data were downloaded monthly and summary scores were calculated for each participant to track adherence throughout the course of the study. For the purposes of this study, adherence was measured as a dichotomous variable of 90% or greater adherence to all doses during the 30 day period before each evaluation visit (24 and 48 weeks). The 90% adherence cutoff point was used because it was determined to be the most clinically relevant to prevent disease progression, transmission, and suppress viral load (Gifford et al., 2000; Harrigan et al., 2005; Moore, Keruly, Gebo, & Lucas, 2005; Department of Health and Human Services, 2008).

CHAPTER 4

ANALYSES

Preliminary Analyses

Prior to testing the mediation model, descriptive statistics were used to describe sample characteristics (i.e., age, ethnicity, education level, SES, etc.). A one-way analysis of variance (ANOVA) was used to determine any group differences in baseline variables between the three intervention groups. To determine the best represented constructs for use in our mediation model, an initial analysis was conducted to test the measurement invariance for each latent construct. A principal components analysis (PCA) was used to reduce the number of mediator variables that represented the constructs in the IMB model. The analysis included the total scale scores for each measure to extract latent constructs to determine an initial structure for investigation.

Prior to conducting the PCA, appropriateness of the data was assessed using the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) statistic, an anti-image correlation matrix, and Bartlett's Test of Sphericity. Specific distributional assumptions were not required for data reduction purposes because conducting a principal components analysis makes no distributional assumptions and normal distributions are not required (Linting, Meulman, Groenen, & Van der Kooij, 2007). The value of the KMO statistic was used to examine appropriateness of the data for factor analysis. Values less than 0.50 are considered unacceptable and indicate that the data are not appropriate for factor analysis (Kaiser, 1974). Values between 0.50 and 0.70 are considered mediocre, values between 0.70 and 0.80 are good, values between 0.80 and 0.90 are great, and values greater than 0.90 are superb (Hutcheson & Sofroniou, 1999). If the value of the KMO statistic was less than 0.50, we examined the Anti-Image Correlation Matrix.

Diagonal values of the Anti-image Correlation Matrix are produced by the KMO statistic and indicate which variables should be considered for removal (Field, 2013). Any variable with a value less than 0.50 was removed from the analysis. Bartlett's Test of Sphericity was used to ensure that there are correlations in the data that indicate that the data were appropriate for factor analysis. This test generated an intercorrelation matrix which calculate the collinearity of the variables. If the intercorrelation matrix is an identity matrix (the correlation of every variable with itself is equal to one and the off-diagonal values are all equal to zero), this would indicate that there was no collinearity among the variables and the data would not be appropriate for factor analysis. A significant value ($p < 0.05$) for the Bartlett's Test of Sphericity indicate that the intercorrelation matrix is not an identity matrix and that the data are appropriate for factor analysis (Field, 2013). Once the KMO statistic is greater than 0.50 and the value of the Bartlett's Test of Sphericity is significant, the data can be used for factor analysis.

A Principle Component Analysis (PCA) with Promax rotation was used as the extraction method because the IMB constructs were expected to correlate (Gorsuch, 1983). Latent constructs were determined by examining the loadings in the Component Matrix. Observed variables that have adequate (0.50 or better) loadings and no cross-loadings between components in the Component Matrix were retained and considered for each latent construct. Variables that loaded on more than one component were examined individually. In general, they were retained on the component where they evidence the highest loading, but conceptual considerations of their fit with the other items in a component were also taken into consideration by examining the content of each item. Variables that did not load well (< 0.40) on any component were considered for removal or retained individually in the models if there were no other variables to represent the constructs of the IMB model. Common themes and latent constructs were identified

by examining the variables that loaded on these components. The number of latent constructs were determined by examining the number of components with eigenvalues greater than 1 in the scree plot, construct validity of each component, and the variance explained by each component.

Once the number of latent constructs were determined, a confirmatory factor analysis (CFA) was conducted using Mplus version 6.11 for each latent construct. A CFA was used to examine measurement invariance to demonstrate that the psychometric properties of the observed variables were generalizable over time (e.g. the same constructs are being measured over time; Horn & McArdle, 1992; Meredith, 1993). Measurement invariance can be established by conducting a series of tests.

The first test was to conduct an omnibus test of equality to assess if the covariance matrices and mean structures are equal across time points. If the matrices did not differ between time points, this provided support for invariance and there was no need to proceed with further invariance testing. If the matrices differed, additional testing was required starting with an unconstrained model progressing to more restricted models until the most appropriate level of invariance has been identified (Little, Preacher, Selig, & Card, 2007). The paths of the retained variables were specified to load onto their respective latent constructs (e.g., motivation related variables were specified to load onto adherence motivation; Bandalos, 1997; Kline, 2005) and error from the same variables were correlated across time (See Figure 3). Equality constraints were applied to identify the level of invariance which include configural, metric, scalar, and residual.

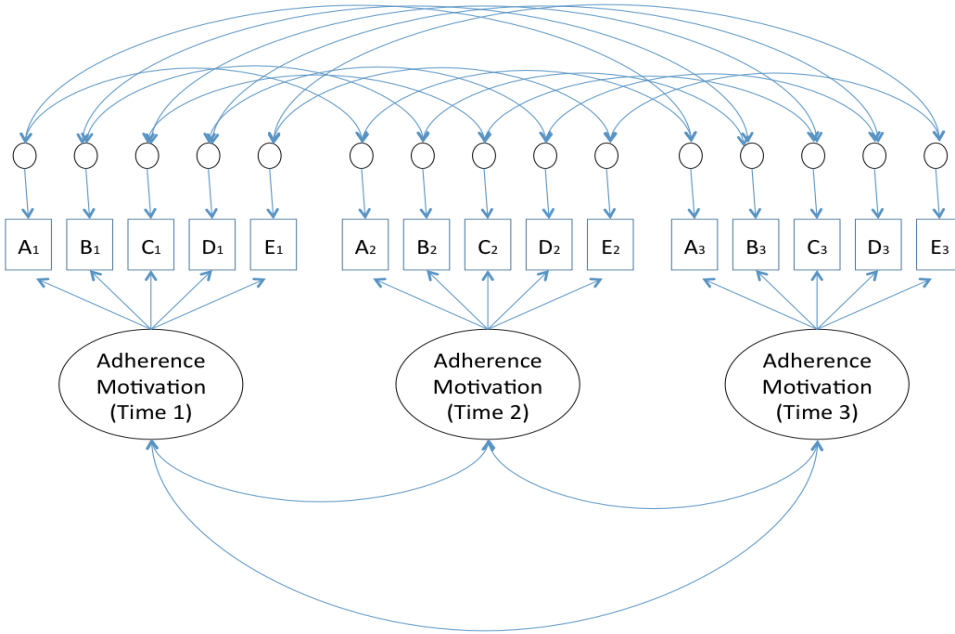


Figure 3. Testing invariance of adherence motivation over time

To identify the most appropriate level of invariance, model fit was examined using Chi-Square (X^2), relative X^2 (X^2/df), root mean square error of approximation (RMSEA), comparative fit index (CFI; Bentler, 1990), and standardized root mean square residual (SRMR). The X^2 value (also known as the discrepancy function, likelihood ratio chi-square, or chi-square goodness of fit) is a measure to assess overall model fit to determine whether the model fits the data well. A model with good fit would produce an insignificant X^2 value ($p > 0.05$; Kline, 2005). However sample sizes greater than 200 are likely to produce a larger X^2 value that is more likely to be significant erroneously suggesting poor model fit (Schumaker & Lomax, 2004; Tanaka, 1993). Additionally, the X^2 value is also affected by model size (value increases with more variables included in a model) and the distribution of the variables (value increases with highly skewed and kurtotic variables). The relative X^2 value is less sensitive to sample size but encompasses similar problems of the X^2 test. Moreover, it is unclear what value would indicate acceptable model fit. Researchers have recommended values as low as two (Byrne, 1998; Tabachnick & Fidell, 2001) and as high as five to indicate reasonable fit (Marsh & Hocevar,

1985). Although the X^2 and relative X^2 tests have severe limitations, they continue to be commonly reported fit statistics (Hooper, Coughlan, & Mullen, 2008).

Alternative indices were also used to assess model fit that are not sensitive to sample size and do not assume multivariate normality. The RMSEA is a measure of lack of fit, where values below 0.08 indicate acceptable fit and below 0.05 indicate excellent fit (Hu & Bentler, 1995).

The RMSEA has been referred to as ‘one of the most informative fit indices’ (Diamantopoulos & Siguaw, 2000) because of its sensitivity to the number of estimated parameters in the model.

The RMSEA will select the most parsimonious model, that is, the one with the fewest number of parameters (Hooper, Coughlan, & Mullen, 2008). Further, another advantage of the RMSEA is that it produces a confidence interval around its value (MacCallum et al., 1996) based on the known distribution values of the statistic which allows the null hypothesis (poor fit) to be tested more precisely (McQuitty, 2004).

Comparative fit index values above 0.90 or 0.95 indicate acceptable and excellent fit, respectively. The CFI takes into account sample size (Byrne, 1998) and produces a model fit estimate that performs well even when the sample size is small (Tabachnick & Fidell, 2001). This index is included in all SEM programs and is one of the most commonly reported fit indices because it is one of the measures that is least affected by sample size (Fan et al, 1999). The SRMR is an absolute measure of fit and values less than .08 are considered to represent good fit (Hu & Bentler, 1999). It is the square root of the difference between the residuals of the sample covariance matrix and the hypothesized covariance model and is more meaningful and easier to interpret than the root mean square residual (RMR; Hooper, Coughlan, & Mullen, 2008).

Primary Analyses

Once invariance and adequate model fit were determined, a multilevel, multiple mediation design was used to determine the indirect effects on adherence through the invariant latent constructs found in the preliminary analysis. Following the recommendation of Preacher, Zhang, and Zyphur, (2010), mediation was assessed using a multilevel mediation model because the data are clustered at the group level. If data were analyzed at the individual level and clustering for each intervention group (MI-CBT/mDOT, MI-CBT, or SC) were ignored, an inflation of type I error may occur (Krull & MacKinnon, 1999; 2001). Moreover, it may be possible that the mechanism that mediates effects at the group level is different from the mechanism that mediates effects at the individual level.

In Project MOTIV8, the intervention was assessed at the group level and the mediators and adherence were assessed at the individual level. As such, a 2-1-1 design was used to assess mediation. Additionally, as recommended by Preacher and Hayes (2008), multiple mediators were examined simultaneously. Advantages to specifying and testing a single multiple mediation model compared to separate simple mediation models include the: possibility to determine the extent to which specific variables mediate the relationship between independent and outcome variables, reduced likelihood of parameter bias, and ability to determine the magnitude of specific indirect effects associated with all mediators.

Specific indirect effects of intervention group on adherence were calculated using the product-of-coefficients approach also called the Sobel test (Sobel, 1982, 1986). The formula for specific indirect effects in a multiple mediator model is the same as the formula used in single-mediator models (Preacher & Hayes, 2008). For example, the indirect effect of group on adherence through a mediator is calculated by the product (ab) of the unstandardized paths

linking group to the mediator (a) and mediator to adherence (b). The total indirect effect of group on adherence is the sum of the specific indirect effects, $\Sigma_i(a_i b_i)$, $i = 1$ to 3 (See Figure 4).

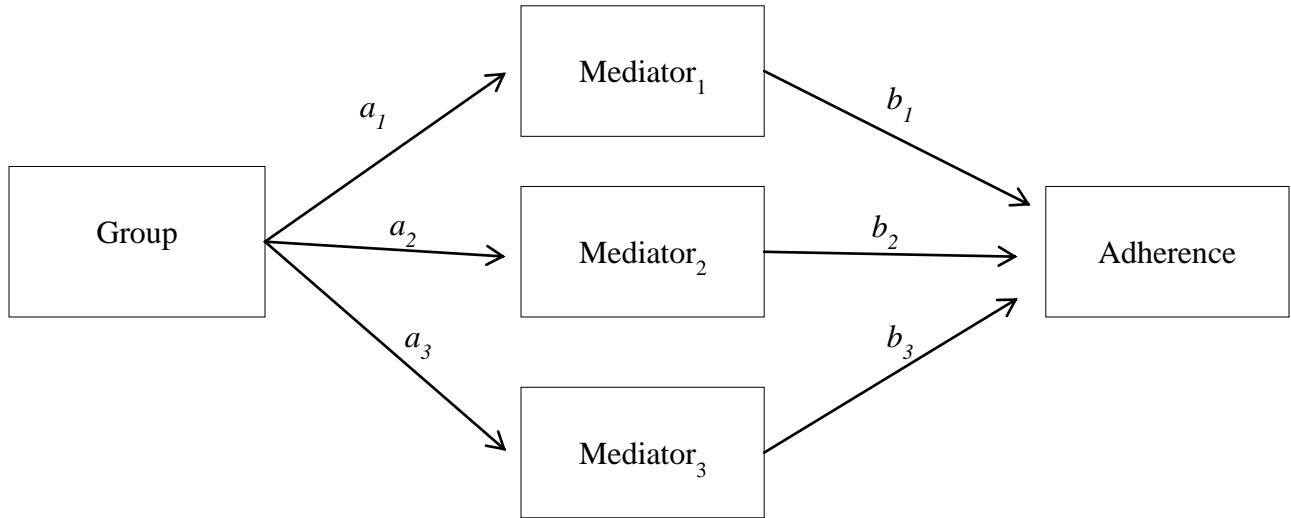


Figure 4. Illustration of a multiple mediation design with three mediators

Following the recommendations of Hayes and Preacher (2013), indicator coding was used to dummy code the three intervention groups to represent comparisons of interest to allow for simultaneous hypothesis testing. The three levels were transformed into two variables: Contrast 1 and Contrast 2. Contrast 1 compared the two treatment conditions with SC. MI-CBT and MI-CBT/mDOT were given values of 0.33 and SC was given a value of -0.67. Contrast 2 compared MI-CBT/mDOT and MI-CBT by assigning the value of 0.5 and -0.5, respectively. Indirect effects were assessed by calculating the product (ab) of the unstandardized paths linking each contrast code to the mediator (a) and mediator to adherence (b). The total indirect effect of group on adherence is the sum of the specific indirect effects, $\Sigma_i(a_i b_i)$, $i = 1$ to 3 (See Figure 5). Mplus was used to calculate the variance, standard error, and odds ratios to determine statistical significance. Significant indirect effects indicated which mediators were impacted by treatment and which mediators impacted adherence.

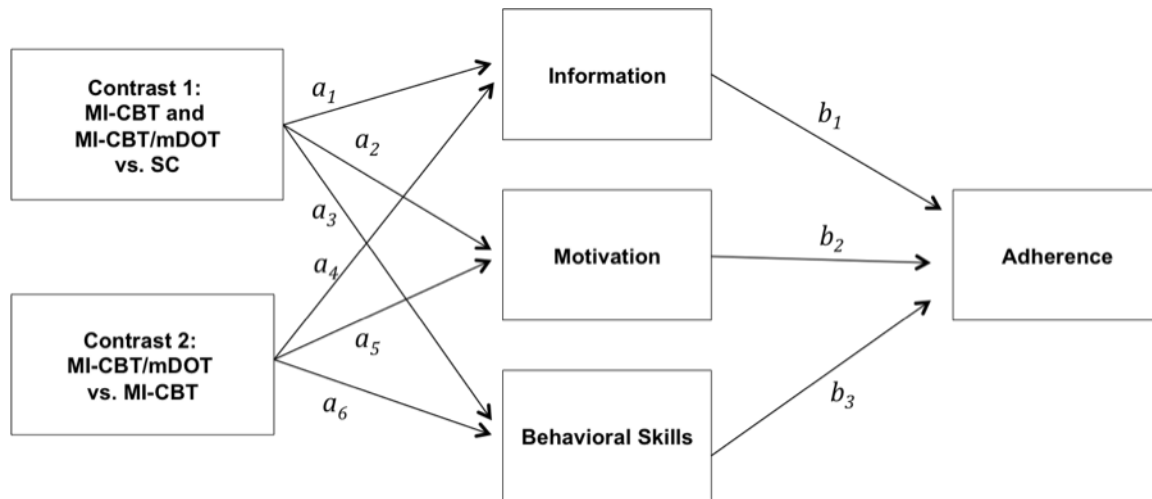


Figure 5. Mediation model examining Information Motivation Behavior Skills constructs as mediators between condition and adherence

CHAPTER 5

RESULTS

Preliminary Analyses

To describe sample characteristics, descriptive statistics for demographic and IMB based mediator variables were assessed. Demographic characteristics ($n = 204$) are shown in Table 2. Participant ages ranged from 18-65 ($M = 40.37$, $SD = 9.56$). Seventy-six percent ($n = 155$) identified their gender as male at birth. The majority of the participants identified themselves as African American (57%) or white (31%). The education of participants varied widely; about 22.5% ($n = 46$) did not have a high school degree, 30% ($n = 62$, 60) of participants had obtained a high school degree/GED or some college training, about 9% ($n = 18$) had a college degree, and a little less than 2% ($n = 3$) had a graduate degree.

Table 2. *Characteristics of Study Participants*

<i>Variable</i>	<i>Study Participants (n = 204)</i>
	<i>n(%)</i>
Gender	
Female	49(24)
Male	155(76)
Race	
African American	116(56.9)
White	64(31.4)
Hispanic or Latino	19(9.3)
American Indian/Alaskan Native	5(2.5)
More than 1 race	14(6.9)
Education	
< High School	46(22.5)
High School/GED	62(30.4)
College Degree	18(8.8)
Graduate Degree	3(1.5)
Estimated Monthly Income	
0-1000	125(61.2)
1001-2000	36(17.6)
2001-3000	15(7.4)
> 3000	9(4.4)

Overall, participants were highly motivated to adhere, had high levels of self-efficacy for adherence, and reported they were most likely to not adhere because of patient related factors (e.g., being away from home). Descriptive statistics for mediator variables are shown in Table 3.

Table 3. *Descriptive Statistics for Mediator Variables*

Mediator Variable	Baseline <i>M (SD)</i>	24 weeks <i>M (SD)</i>	48 weeks <i>M (SD)</i>
Information related variables			
Knowledge about ART	8.89 (1.86)	9.39 (1.77)	9.28 (1.96)
ART medical knowledge	.190 (.12)	.201 (.12)	.204 (.13)
Motivation related variables			
Motivation to adhere	9.34 (1.08)	9.29 (1.35)	9.46 (1.09)
Autonomous motivation	6.71 (.55)	6.66 (.81)	6.69 (.74)
Controlled motivation	4.43 (1.63)	4.48 (1.66)	4.62 (1.69)
Autonomy support from providers	6.46 (.78)	6.52 (.89)	6.55 (.90)
Necessity for adherence	3.99 (.74)	4.01 (.82)	4.10 (.78)
Concern for adherence	2.82 (.82)	2.41 (.79)	2.38 (.89)
Social support for adherence	1.69 (.74)	1.57 (.89)	1.53 (.88)
Behavioral skill related variables			
Self-efficacy to adhere	8.20 (1.6)	8.38 (1.69)	8.87 (1.39)
Patient related reasons for nonadherence	4.54 (5.14)	-	3.45 (3.95)
Logistical related reasons for nonadherence	1.35 (2.51)	-	1.02 (2.19)
Medication related reasons for nonadherence	3.86 (4.99)	-	2.11 (3.86)
Perceived difficulty of regime	1.70 (.76)	1.42 (.63)	1.40 (.68)

A one-way analysis of variance (ANOVA) was conducted to determine whether there were significant group differences in baseline mediator variables between the three intervention groups. Results revealed no significant differences between the groups (see Table 4).

Table 4. *One-way ANOVA Examining Group Differences in Baseline Mediator Variables*

Mediator Variable	<i>Df</i>	<i>F</i>	χ^2	<i>p</i>
Information related variables				
Knowledge about ART	2	1.55	.03	.22
ART medical knowledge	2	2.65	.05	.08
Motivation related variables				
Motivation to adhere	2	1.23	.02	.29
Autonomous motivation	2	.05	.00	.95
Controlled motivation	2	.16	.00	.85
Autonomy support from providers	2	.20	.00	.82
Necessity for adherence	2	.26	.01	.78
Concern for adherence	2	.19	.00	.83
Social support for adherence	2	.99	.02	.38
Behavioral skill related variables				
Self-efficacy to adhere	2	.50	.01	.61
Patient reasons for nonadherence	2	.95	.02	.39
Logistic reasons for nonadherence	2	.56	.01	.57
Medication reasons for nonadherence	2	2.41	.05	.09
Perceived difficulty of regime	2	.65	.01	.53

Prior to the main analysis, a PCA was used as a data reduction technique to extract latent constructs from 14 observed variables. Latent constructs were identified by examining the variables that loaded to the components. Hypothesized constructs and variables are presented in Table 5.

Table 5. Observed Variables Assessed in PCA

Information related variables
1. Knowledge about ART
2. ART medical knowledge
Motivation related variables
3. Motivation to adhere
4. Autonomous motivation
5. Controlled motivation
6. Autonomy support from providers
7. Necessity for adherence
8. Concern for adherence
9. Social support
Behavioral skill related variables
10. Self-efficacy to adhere
11. Patient related reasons for nonadherence
12. Logistical related reasons for nonadherence
13. Medication related reasons for nonadherence
14. Perceived difficulty of regime

Prior to conducting the PCA to identify latent constructs, appropriateness of the data was assessed using the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) statistic and Bartlett's Test of Sphericity. The KMO statistic was above the recommended value of 0.50 and Bartlett's Test of Sphericity was significant for each time point of the study indicating that correlations in the data were appropriate for conducting factor analyses (see Table 6). Given these overall indicators, all mediator variables were retained and used to conduct factor analyses.

Table 6. *KMO Statistic and Bartlett's Test of Sphericity at Each Time Point*

Time	KMO Statistic	<i>Df</i>	X^2	<i>p</i>
Baseline	.74	91	813.34	<.001
Week 24	.81	55	601.43	<.001
Week 48	.75	91	662.80	< .001

A PCA with Promax rotation was used as the extraction method for data collected at baseline, week 24, and week 48. Latent constructs were determined by examining the eigenvalues in the scree plot, the variance explained by each factor, the factor loadings, and construct validity.

Factor Structure for Baseline Data

There were four factors that had eigenvalues ≥ 1 . The first factor explained 25% of the variance, the second factor explained 16% of the variance, and a third factor explained 11% of the variance. The fourth component had an eigenvalue equal to 1 and explained 7% of the variance. The four factor solution which explained 59% of the variance was retained because of previous theoretical support, sufficient number of primary loadings (> 0.50), the “leveling off” of factors with eigenvalues > 1 in the scree plot, and ease of interpreting the fourth factor. One variable (amount of perceived social support) was eliminated because it failed to meet the minimum criteria of having a primary factor loading ≥ 0.40 . The Information, Motivation, and Behavioral Skills constructs from the IMB model were identified, and a fourth factor which encompassed concerns about adherence and perceived difficulty of regime was also identified. Two observed variables (knowledge about ART and ART medication knowledge) composed the information factor. Five observed variables (motivation to adhere, autonomous motivation, self-efficacy to adhere, autonomy support from providers, and necessity for adherence) composed the

motivation factor. Three observed variables (patient reasons, medication related, and logistic reasons for nonadherence) composed the behavioral skills factor. Lastly, three observed variables (concern for adherence, perceived difficulty of adherence, and control motivation) composed the fourth factor.

To determine changes in the factor structure after removing the amount of perceived social support, a PCA of the remaining 13 mediator variables using Promax rotation was conducted. There were no changes in the factor structure as four factors had eigenvalues ≥ 1 and the same observed variables composed each of the four factors. The amount of variance explained by the four factor structure explained 62% of the variance. All variables had loadings > 0.50 and only two variables had a cross-loading > 0.40 (beliefs related to the necessity of ART, perceived difficulty of regime), however these two variables had a primary loading of 0.52 and 0.58, respectively, and were retained on their primary factors. The factor loading matrix for the final solution of baseline mediator variables is shown in Table 7.

Table 7. *Factor loadings based on a PCA with Promax Rotation for 13 baseline mediator variables*

	ART Information	Adherence Motivation	Adherence Behavioral Skills	Negative Adherence Beliefs
Knowledge about ART	.79			
ART medication knowledge	.78			
Motivation to adhere		.78		
Autonomous motivation		.76		
Self-efficacy to adhere		.71		
Autonomy support from providers		.64		
Necessity for adherence		.52		
Patient reasons for nonadherence			.93	
Medication reasons for nonadherence			.91	
Logistical reasons for nonadherence			.78	
Concerns for adherence				.81
Perceived difficulty of regime				.58
Controlled motivation				.52

Factor Structure for Week 24 Data

There were three factors that had eigenvalues ≥ 1 . The first factor explained 34% of the variance, the second factor explained 12% of the variance, and a third factor explained 11% of the variance. The three factor solution which explained 57% of the variance was retained over a four factor solution because of previous theoretical support, sufficient number of primary loadings (> 0.50), and the “leveling off” of the number of factors with eigenvalues greater than 1 in the scree plot. Similarly to the results of the PCA found using baseline data, amount of perceived social support was eliminated. This observed variable did not belong conceptually with the information factor and had a weak primary loading (0.45). Three variables (patient, medication related, and logistic reasons for nonadherence) were not measured at this time point and were not included in the PCA. The information, motivation, and behavioral skills constructs from the IMB mode were identified. Two observed variables (knowledge about ART and ART

medication knowledge) composed the information factor. Six observed variables (motivation to adhere, autonomous motivation, self-efficacy to adhere, autonomy support from providers, perceived difficulty of regime, and concern for adherence) composed the motivation factor. Two observed variables (control motivation and necessity for adherence) composed the behavioral skills factor.

To determine changes in the factor structure after removing the amount of perceived social support, a PCA of the remaining 10 mediator variables using Promax rotation was conducted. There were three factors that had eigenvalues ≥ 1 and all observed variables loaded on the same factors except for concern for adherence which had a weak loading (0.47) on the behavioral skills factor. The three factor solution explained 67% of the variance. There were no cross-loadings > 0.40 . The factor loading matrix for the final solution of week 24 mediator variables is shown in Table 8.

Table 8. *Factor loadings based on a PCA with Promax Rotation for 10 mediator variables at Week 24*

	ART Information	Adherence Motivation	Adherence Behavioral Skills	Negative Adherence Beliefs
Knowledge about ART	.77			
ART medication knowledge	.75			
Motivation to adhere		.90		
Autonomous motivation		.81		
Self-efficacy to adhere		.85		
Autonomy support from providers		.77		
Necessity for adherence				.53
Patient reasons for nonadherence				
Medication reasons for nonadherence				
Logistical reasons for nonadherence				
Concerns for adherence				.47
Perceived difficulty of regime		-.66		
Controlled motivation				.74

Factor Structure for Week 48 Data

There were four factors that had eigenvalues ≥ 1 . The first factor explained 27% of the variance, the second factor explained 15% of the variance, and a third and fourth factor explained 9% of the variance. The three factor solution which explained 52% of the variance was retained because of previous theoretical support, sufficient number of primary loadings (> 0.50), the “leveling off” of factors with eigenvalues greater than 1 in the scree plot, and difficulty interpreting the fourth factor. Similarly to the results of the PCA found using baseline and week 24 data, amount of perceived social support was eliminated. This observed variable failed to meet the criteria of fitting conceptually with the factor on which loaded. The information, motivation, and behavioral skills constructs from the IMB mode were identified. Two observed variables (ART medication knowledge and perceived difficulty of regime) composed the information factor. Five observed variables (motivation to adhere, autonomous motivation, self-

efficacy to adhere, autonomy support from providers, and necessity for adherence) composed the motivation factor. Five observed variables (medication reasons for nonadherence, patient reasons for nonadherence, logistic reasons for nonadherence, control motivation, and knowledge about ART) composed the behavioral skills factor.

To determine changes in the factor structure after removing the amount of perceived social support, a PCA of the remaining 13 mediator variables using Promax rotation was conducted. There were three factors that had eigenvalues ≥ 1 and all observed variables loaded on the same factors except for control motivation which had a weak loading (0.33) to the motivation factor and was eliminated. To determine changes in the factor structure after removing control motivation, a PCA of the remaining 12 mediator variables using Promax rotation was conducted. There were three factors that had eigenvalues ≥ 1 and all observed variables loaded on the same factors. A three factor solution explained 59% of the variance. All observed variables had loadings > 0.50 and only two variables had a cross-loading > 0.40 (self-efficacy for adherence and perceived difficulty of regime), however these two variables had a primary loading of 0.77 and 0.65, respectively, and were retained on their primary components. The factor loading matrix for the final solution of week 48 mediator variables is shown in Table 9.

Table 9. *Factor loadings based on a PCA with Promax Rotation for 12 mediator variables at Week 48*

	ART Information	Adherence Motivation	Adherence Behavioral Skills	Negative Adherence Beliefs
Knowledge about ART			-.54	
ART medication knowledge	.75			
Motivation to adhere		.85		
Autonomous motivation		.77		
Self-efficacy to adhere		.75		
Autonomy support from providers		.64		
Necessity for adherence		.51		
Patient reasons for nonadherence			.79	
Medication reasons for nonadherence			.88	
Logistical reasons for nonadherence			.73	
Concerns for adherence			.64	
Perceived difficulty of regime	.65			

Measurement and Structural Invariance

To determine if the Information-Motivation-Behavioral Skills constructs (Fisher & Fisher, 1992) found in the preliminary PCA had measurement invariance and structural invariance over time (i.e., at baseline, week 24, and week 48), a confirmatory factor analysis (CFA) was conducted using Mplus v. 6.12 (Muthén & Muthén, 1998-2011). Maximum likelihood (ML) estimation was used for all analyses because it has been shown to be robust to nonnormality (Muthén & Muthén, 2009). Nested model comparisons were conducted using a combination of fit indices including the difference in the model χ^2 values, RMSEA, CFI, and SRMR.

Configural Invariance

Initially, a configural invariance model was specified in which three correlated factors (i.e., the factor at three occasions) were estimated simultaneously. Following recommendations of Muthen and Muthen (1998) the second indicator's loading was fixed to 1 and its intercept was fixed to 0 for each factor to identify the model. All factor variances, covariances, and means

were then estimated with the exclusion of the observed controlled motivation variable (as determined by the preliminary PCA). The configural invariance model had acceptable fit. The modification indices suggested that ART medication knowledge was the largest source of the misfit and should be excluded. After doing so, the configural invariance model fit significantly better than the initial configural invariance model, $\Delta\chi^2(87) = 137.22, p < .001$. Model fit indices revealed good model fit (RMSEA = 0.057 90% CI = 0.049-0.066, CFI = .912, SRMR = .080). The analysis proceeded by applying parameter constraints in successive models to examine potential decreases in fit resulting from measurement or structural non-invariance over the three occasions.

Metric Invariance

Equality of the indicator factor loadings across three occasions was then examined in a metric invariance model. All factor loadings were constrained equal across time; all intercepts (except for the second item) and residual variances were still permitted to vary across time. Factor covariances and residual covariances were estimated as described previously. The metric invariance model did not fit any less well than the configural invariance model $\Delta\chi^2(73) = 89.4, p > .05$. The modification indices suggested that the loading of perceived difficulty of regime was a source of misfit and should be freed. After doing so, the partial metric invariance model fit significantly better than the full metric invariance model, $\Delta\chi^2(1) = 29.32, p < .05$. Alternative fit indices revealed adequate model fit (RMSEA = 0.057 90% CI = 0.049-0.065, CFI = .91). The fact that metric invariance (i.e., “weak invariance”) held indicates that the indicators were related to the latent factor equivalently across time, or more simply, that the same latent factor was being measured at each occasion (with the exception of controlled motivation and ART medication knowledge).

Scalar Invariance

Equality of the unstandardized indicator intercepts across time was then examined in a scalar invariance model. All factor loadings and indicator intercepts were constrained equal across time (except for controlled motivation, ART medication knowledge, and perceived difficulty of regime at time 3); all residual variances were still permitted to differ across time. Factor covariances and residual covariances were estimated as described previously. The scalar invariance model fit significantly better than the partial metric invariance model, $\Delta\chi^2(13) = 58.99$, $p < .001$. Alternative fit indices demonstrated adequate model fit (RMSEA = 0.062 90% CI = 0.054-0.069, SRMR = .090). The fact that scalar invariance (i.e., “strong invariance”) held indicate that week 24 and 48 data have the same expected response for each indicator at the level of the trait, and that the observed differences in the indicator means between week 24 and 48 are due to factor mean differences only.

Residual Invariance

Equality of the unstandardized residual variances across time was then examined in a residual variance invariance model. All factor loadings, item intercepts, and residual variances (except for control motivation, ART medication knowledge, and perceived difficulty of regime) were constrained to be equal across groups. Factor covariances and residual covariances were estimated as described previously. The residual variance invariance model did not fit better than the last scalar invariance model, $\Delta\chi^2(16) = 20.89$, $p > .05$. The fact that residual variance invariance (i.e., “strict invariance”) did not hold indicates that the amount of indicator residual variance was not the same across weeks 24 and 48.

In conclusion, these analyses showed that partial measurement invariance was obtained over time. The relationships of the indicators to the latent factors of the IMB model were

equivalent at week 24 and 48. These analyses also revealed that partial structural invariance was obtained over time, such that the same amount of individual differences variance in IMB constructs was observed with equal covariance over time across occasions. Model fit indices for all models are given in Table 10. The observed variables that comprised each latent construct are listed in Table 11.

Table 10. *Model fit summary of measurement and structural invariance testing*

	χ^2 (df)	CFI	SRMR	RMSEA (90 % CI)	$\Delta\chi^2$ (df)	Δ CFI	Δ RMSEA
Configural	721.92 (437)	.899	.083	.057 (.049-.064)	-	-	-
Partial Configural	584.70 (350)	.912	.080	.057 (.049-.066)	-137.22 (87)	.013	0
Metric	632.52 (364)	.899	.090	.060 (.052-.068)	47.82 (14)	-.013	.003
Partial Metric	606.20 (363)	.91	.087	.057 (.049-.065)	-26.32 (1)	.01	-.003
Scalar	665.20 (376)	.89	.09	.062 (.054-.069)	58.99 (13)	-.02	.005
Residual	686.10 (392)	.89	.14	.06 (.053-.068)	20.90 (16)	0	-.001

Table 11. *Observed variables included in invariant IMB constructs*

Information	Motivation	Behavior Skills (48 weeks only)
Concern for adherence	Motivation to adhere	Patient reasons for nonadherence
Knowledge about ART	Autonomous motivation	Medication reasons for nonadherence
Perceived Difficulty of Regime	Self-efficacy to adhere	Logistical reasons for nonadherence
	Autonomy support from providers	
	Necessity for adherence	

Primary Analysis

Following the recommendation of Preacher, Zhang, and Zyphur (2010) mediation was assessed using a multilevel mediation model. A 2-1-1 design was used to assess mediation and multiple mediators were examined simultaneously (Preacher & Hayes, 2008). Indicator coding was used to dummy code the three intervention groups to represent comparisons of interest to

allow for simultaneous hypothesis testing (Hayes & Preacher, 2013). The three levels were transformed into two variables: Contrast 1 and Contrast 2. Contrast 1 compared SC with the other two groups assigning the value of -0.667 to SC and the other two groups were given a value of 0.333. Contrast 2 compared MI-CBT and MI-CBT/mDOT by assigning the value of -0.5 and 0.5, respectively. As recommended, values were kept within 1 to ease interpretation (Hayes & Preacher, 2013). Potential mediators were self-reported information, motivation, and behavioral skill factors. However the behavioral skill construct was only assessed for 48 week data as there was no behavioral skill construct that was found to be invariant for 24 week data because reasons for nonadherence was not measured at this time point.

To test the mediated effects, a multicategorical, multiple mediator path model using MLR estimator was conducted. Mplus was used to calculate the variance, standard error, and odds ratios for the indirect effects to determine statistical significance. Significant indirect effects indicated which mediators were impacted by treatment and which mediators impacted adherence. As shown in Figure 6, the path models included: (1) paths between the intervention group and potential mediators, and (2) paths from the potential mediators to adherence.

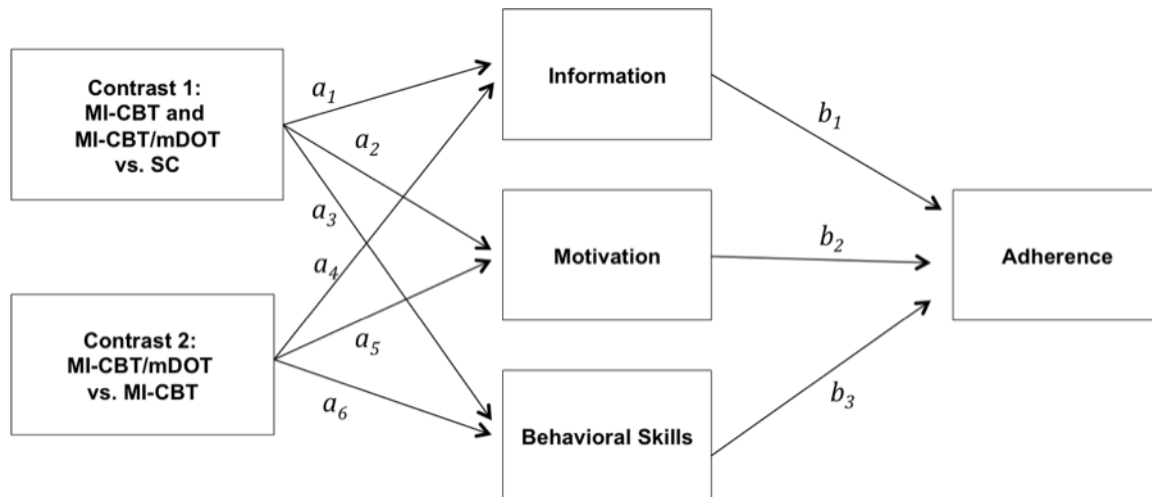


Figure 6. Conceptual mediation model

Mediational Models

The first model examined the effect that occurred to week 24 information and motivation constructs as a result of the intervention and simultaneously assessed the potential mediator effects on week 24 adherence. The estimated model is shown in Figure 7.

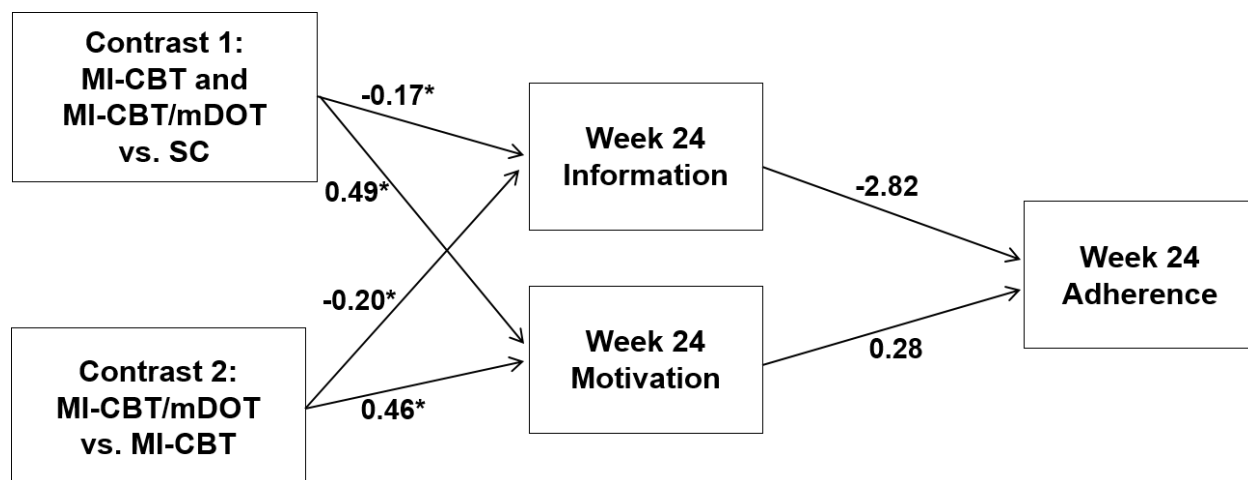


Figure 7. Mediation model examining the information and motivation constructs as mediators between intervention and week 24 adherence. All parameter estimates are unstandardized. SC = standard care; MI-CBT = motivational interviewing-cognitive behavioral therapy only; MI-CBT/mDOT = motivational interviewing-cognitive behavioral therapy with modified directly observed therapy. $*p < 0.05$

A significant intervention effect on information was found for both contrasts, as participants in the treatment conditions were less likely to have adherence information than participants in the SC condition, ($b = -0.17$, $SE = 0.075$, $\beta = -0.25$, $p < .05$), and participants who received MI-CBT with mDOT were also less likely to have adherence information than participants who received MI-CBT only, ($b = -0.20$, $SE = 0.09$, $\beta = -0.25$, $p = .01$). A significant intervention effect was also found on motivation, as participants in the treatment conditions were more likely to have motivation to adhere than participants in the SC condition, ($b = 0.49$, $SE = 0.21$, $\beta = 0.18$, $p < .05$), and participants who received MI-CBT with mDOT were also more likely to have motivation to adhere than participants who received MI-CBT only, ($b = 0.46$, $SE = 0.23$, $\beta = 0.15$, $p < .05$). No significant effects were found on week 24 adherence.

To better understand the significant intervention effects found for contrast 1, an additional model examined the effect on week 24 information and motivation between each

treatment condition and SC (see Figure 8). Significant intervention effects on information and motivation were found for contrast 2 (comparing MI-CBT/mDOT and SC), as participants in the MI-CBT/mDOT condition were less likely to have adherence information, ($b = -0.31$, $SE = 0.11$, $\beta = -0.40$, $p < .01$), and more likely to have motivation to adhere than participants in the SC condition, ($b = 0.78$, $SE = 0.27$, $\beta = 0.26$, $p < .01$).

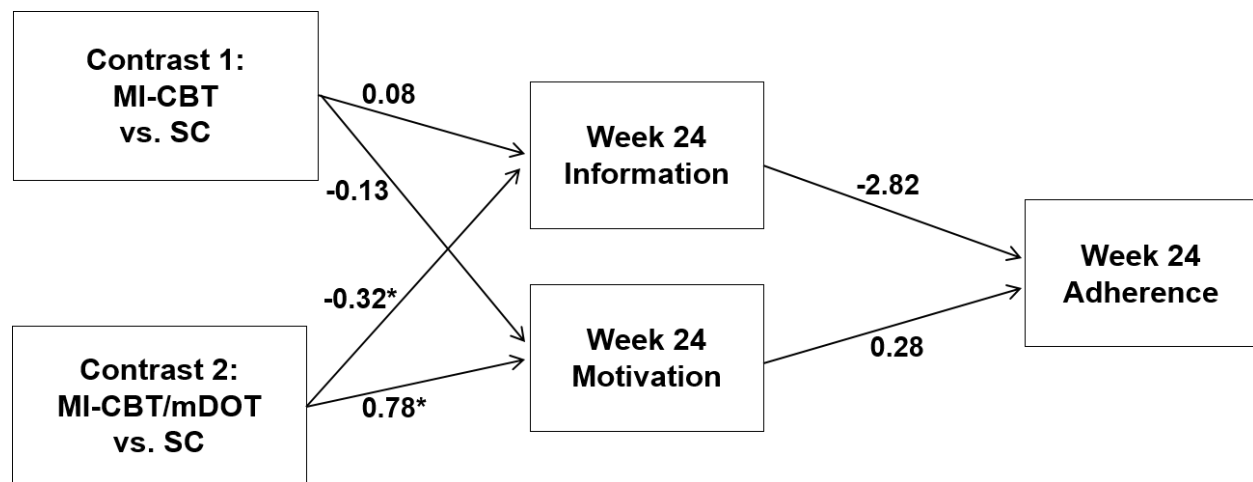


Figure 8. Additional mediational model examining the effect between treatment conditions and SC on information and motivation constructs. All parameter estimates are unstandardized. * $p < 0.05$

The next model examined the effect on week 24 information and motivation constructs as a result of the intervention and simultaneously assessed the potential mediator effects on week 48 adherence. As shown in in Figure 9, the intervention effects were replicated on the information and motivation constructs as shown in the first model. Similarly, no significant effects were found on week 48 adherence.

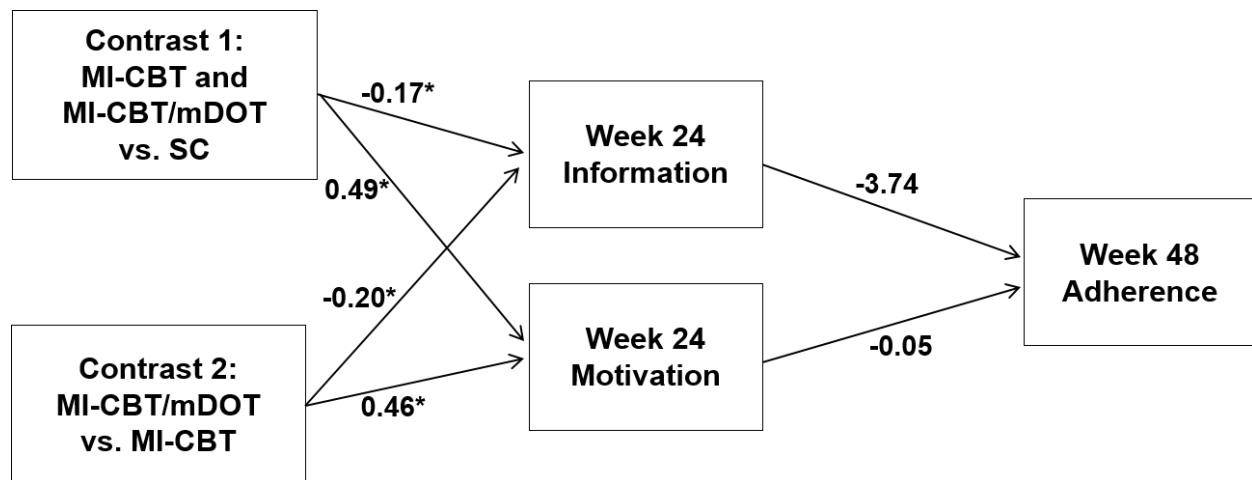


Figure 9. Mediation model examining the information and motivation constructs as mediators between intervention and week 48 adherence. All parameter estimates are unstandardized. * $p < 0.05$

The final model examined the effect on week 48 information, motivation, and behavior skills constructs as a result of the intervention and simultaneously assessed these mediator effects on week 48 adherence. The estimated model is shown in Figure 9. There were no significant effects found as a result of the intervention. However, there was a significant effect between week 48 motivation and adherence, ($b = 0.90$, $SE = 0.45$, $\beta = 0.39$, $p < .05$).

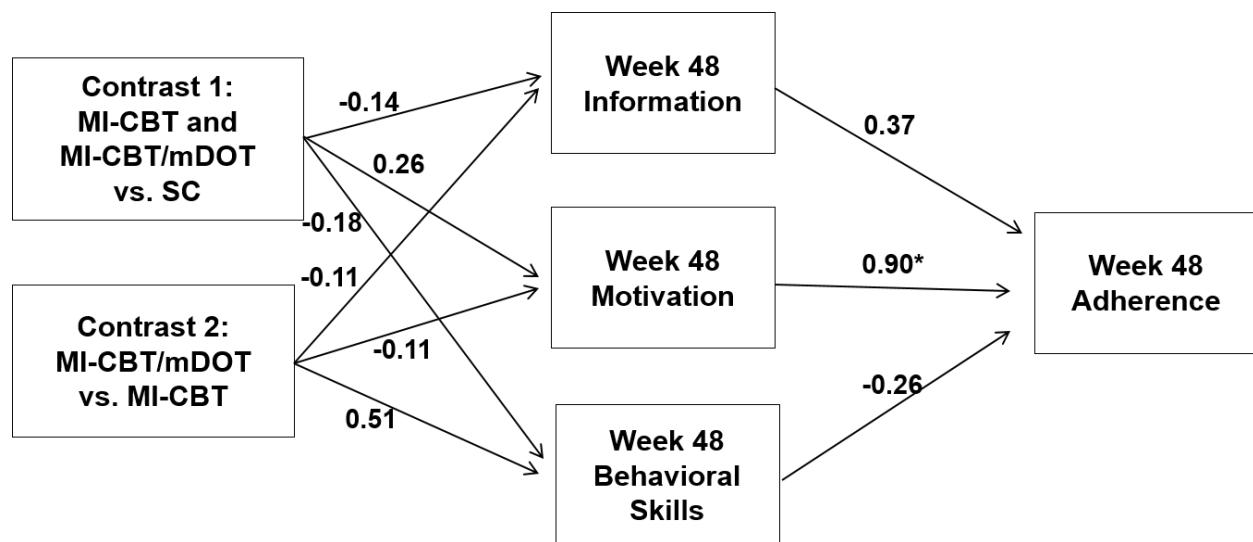


Figure 10. Mediation model examining the information, motivation, and behavioral skills constructs as mediators between intervention and week 48 adherence. All parameter estimates are unstandardized. * $p < 0.05$

CHAPTER 6

DISCUSSION

The preliminary analysis of Project MOTIV8 revealed three constructs that appeared consistent with the IMB model and modification indices that these constructs were stable at baseline and week 48. The adherence information construct consisted of measures of Concerns for Adherence, Knowledge about ART, and Perceived Difficulty of Regime. The adherence motivation construct included the Brief Motivation Scale, Adherence Self-efficacy, Necessity for Adherence, Autonomous Motivation, and Autonomy Support from Providers scales. The behavioral skills construct was not obtained at week 24 due to variables (e.g., Self-efficacy for Adherence and Perceived Difficulty of Regime) failing to load on the construct and additional variables (e.g., Patient, Medication, and Logistical Reasons for Nonadherence) not being measured at this time point. However, the construct was observed at baseline and week 48 and included measures of Patient, Medication, and Logistical Reasons for Nonadherence.

Although the three constructs that emerged are interpreted to be IMB constructs, the failure of some measures to load on the intended construct (e.g., Self-Efficacy to Adhere loading on the motivation rather than the behavioral skills construct and the Concerns for Adherence scale loading on the adherence information construct) suggests that alternative interpretations of the constructs may be valid (e.g., the motivation construct might be a combined motivation/confidence construct and the behavioral skills construct may be a self-report adherence measure). This highlights the difficulty with the lack of established measures for the IMB model. Several studies have used the IMB model as a theoretical foundation to develop interventions, however the methodology used to assess and measure the IMB components have been variable (Leeman, Chang, Voils, Crandell, & Sandelowski, 2011; See Table 12). Few

studies report how IMB constructs are measured. Furthermore, there is little evidence to demonstrate that the measures used to represent IMB constructs are valid and invariant suggesting an area for much needed additional research. These limitations regarding measurement of the IMB constructs should be kept in mind when interpreting the main analyses.

The primary analysis revealed that MI-CBT/mDOT had significant effects on participants' adherence information and motivation at week 24. Unexpectedly participants in the MI-CBT/mDOT condition had lower levels of adherence information relative to participants in the other treatment groups. With respect to motivation MI-CBT/mDOT participants had higher scores than participants in the other groups. There were no significant effects of the mediator variables on adherence at week 24. In addition, the intervention did not affect any of the IMB mediator constructs at week 48. However, adherence motivation at week 48 was significantly related to increased adherence at week 48.

Our results revealed limited intervention effects on the potential mediators, which may be due to unsuccessful intervention strategies. Further, the majority of our potential mediators were not associated with adherence suggesting that our theoretical assumptions about the active components of the intervention were not entirely valid. The IMB model of behavior change (Fisher & Fisher, 1992) suggests that information, motivation, and behavioral skills are critical targets for promoting adherence behavior. Based on this framework, these three constructs were targeted with the assumption that by impacting adherence related information, motivation, and behavioral skills, ART adherence would, in turn, improve.

The use of CBT targeted the adherence information component (e.g., adherence knowledge discussed during counseling session) to enhance knowledge for adherence. However, the results demonstrated that intervention strategies to target adherence information were not

effective. As indicated the combined MI-CBT/mDOT treatment appeared to diminish knowledge of adherence related information. There was also no significant effect of receiving MI-CBT on adherence information relative to SC. The negative effect of MI-CBT/mDOT may have been because participants who received mDOT may have relied on project staff and therefore retained less of the provided adherence information. This is consistent with prior work which indicates the removal of DOT leads to declines in adherence (Berg, Litwin, Li, Heo, & Arnsten, 2011). Participants receiving mDOT may have focused less on adherence related information because they received repeated visits from staff and received cues to take their medications. Nevertheless, MI-CBT's failure to enhance knowledge relative to SC suggests either that SC provided effective knowledge or that MI-CBT was ineffective in enhancing knowledge. Examination of the means for the adherence information scales across all participants suggests that their knowledge about ART did not increase and they did not perceive their regimes to be difficult.

Motivation was targeted with the use of MI techniques in both treatment groups, however the results demonstrated that only the MI-CBT/mDOT condition had a significant effect on levels of adherence motivation. MI-CBT/mDOT enhanced motivation relative to both MI-CBT and SC at week 24 although this effect was not sustained at week 48. The lack of an effect of MI-CBT alone on adherence motivation relative to SC indicates the observed motivational effects in this study were due to the mDOT rather than MI-CBT portion of the treatment. This suggests that daily contact with supportive project staff may have served to enhance participants' motivation for adherence (Bradley-Ewing, Thomson, Pinkston, & Goggin, 2008) over and above any effect of the MI components. Nevertheless, it is surprising that the MI intervention component (alone) did not have a positive effect relative to SC.

Prior research studies that developed IMB based interventions have failed to examine whether motivation mediated the relationship between the intervention and ART adherence. Nevertheless, the broader literature on the effectiveness of MI for increasing motivation and fostering behavior change for adherence (Ingersoll et al., 2011; Parsons, Golub, Rosof, & Holder, 2007; Safren et al., 2001) suggests this finding is anomalous. Perhaps the most likely explanation for the lack of effect found between MI-CBT and motivation is that baseline motivation levels were very high (e.g., $M = 9.34$). This suggests that MI-CBT counseling did not enhance participants' motivation because motivation levels were consistently high throughout the study and there was little room to change or improve motivation. Only the regular direct intervention of staff in the form of mDOT was able to increase already high levels of motivation.

With regard to the effect of the treatments on behavioral skills, our preliminary analysis indicated that self-efficacy for adherence and perceived difficulty of regime variables failed to load on the adherence behavioral skills construct. This suggests that the measures used may not have appropriately represented the adherence behavioral skills construct as hypothesized. As shown in the CFA, self-efficacy for adherence appeared to be reflecting the invariant motivation construct while reasons for nonadherence accurately represented behavioral skills and was invariant at baseline and 48 weeks, but was not measured at week 24. To address measurement concerns, future intervention studies should identify measures that can be used to validly assess behavioral skills and these measures need to be assessed at all key time points.

Due to the lack of invariant measure of behavioral skills that was measured at week 24 the effect of the interventions on behavioral skills could only be examined in the long term. Our results at week 48 suggest the modules focused on enhancing behavioral skills may not have been effective or strong enough to impact participants' skills in the long run, as with the other

two IMB constructs. Because of the lack of available week 24 data it is unclear whether the interventions had any effect in the short run.

To our knowledge, this is the first study to assess the role of potential mediators in an IMB based intervention to improve ART adherence. Few studies have used appropriate statistical techniques to assess mediation in intervention research (Leeman, Chang, Voils, Crandell, & Sandelowski, 2011; Preacher, Zhang, & Zyphur, 2010). More importantly, even fewer studies have evaluated the role of mediators in efficacy studies that have failed to demonstrate significant main effects. To improve the efficacy of interventions, an assessment of theoretical mediators in intervention studies with and without significant effects is necessary to inform future research on effective and ineffective treatment components (Glasgow, 2002; Kraemer et al., 2002).

Although there are no prior studies evaluating the role of potential mediators in IMB based interventions for ART adherence, one prior study used a mixed-methods approach to identify and test potential mediators of ART adherence by integrating results across intervention and quantitative observational studies (Leeman, Chang, Voils, Crandell, & Sandelowski, 2011). Their results suggested that current drug/alcohol use, satisfaction with social support, emotional wellbeing, positive forms of coping, self-efficacy, locus of control, knowledge of HIV treatment, and satisfaction with healthcare provider are all potential mediators of ART adherence interventions. These findings include some IMB related variables but because of the lack of a coherent theoretical framework such as the IMB model it is difficult to reconcile these results with the present study. A recent review of research using the IMB for a variety of health problems included six studies focused on increasing ART adherence for individuals with HIV/AIDS (Margolin, Avants, Warburton, Hawkins, & Shi, 2003; Parsons, Golub, Rosof, &

Holder, 2007; Pearson, Micek et al., 2007; Purcell et al., 2007; Sabin et al., 2010; Wagner et al., 2006). Five of the six studies demonstrated significantly higher adherence for treatment conditions compared to the control conditions and effective intervention techniques included the use of interactive discussion and counseling for the adherence information construct, the use of counseling and MI techniques to enhance personal motivation, and the use of role-playing and skill-building modules to enhance behavioral skills. However, similar to our findings, other studies have failed to impact ART adherence using this model (Purcell et al., 2007; Sampaio-Sa et al., 2008; Wagner et al., 2006). Unfortunately many randomized controlled trials that have developed their interventions based on the IMB model fail to describe how their interventions target the various components of the IMB model and also fail to measure the impact of their intervention on the IMB constructs (see Table 12). Only one study in the review (Margolin, Avants, Warburton, Hawkins, & Shi, 2003) provided information on how they measured the IMB constructs and how these variables were affected pre and post-treatment. Mean values of the IMB variables increased for both treatment conditions over time, however only participants who were in the HIV harm reduction program (HHRP) condition demonstrated significantly more improvements in sex-related and drug-related behavioral skills.

Our findings suggest that Project MOTIV8 may not have been effective at enhancing ART adherence because the novel MI-CBT/mDOT intervention may have included ineffective strategies to target adherence information and behavioral skills or contained other treatment components (i.e., observed therapy) that undermined the effects of these strategies. Given that the CBT has well-established empirical support it may be more plausible that its effects were undermined by the mDOT component. The treatment conditions failed to impact adherence information and adherence behavioral skills were poorly defined and measured. MI-CBT did not

have an effect on motivation suggesting that MI counseling may not be effective for individuals presenting with high levels of motivation. However, mDOT did significantly enhance levels of motivation, but similar to previous research this impact may not have been strong enough to continue after treatment (Berg, Litwin, Li, Heo, & Arnsten, 2011).

In conclusion, our findings suggest that future studies should determine which measures to use to validly and reliably assess IMB constructs and assess whether these constructs are invariant across time. Moreover, it would be desirable to develop objective measures for the assessment of adherence behavioral skills rather than relying on indirect measures that focus on participants' levels of self-efficacy, perceived difficulty of regime, and reasons for nonadherence.

Future intervention studies that plan to use MI-CBT counseling to target motivation should assess participants' baseline levels motivation as MI counseling may not be effective with highly motivated participants. Additionally, mDOT may not be an effective intervention to enhance information or retain motivation as repeated cues may diminish the impact on information and motivation wasn't sustained. Our results suggest that mDOT may not be an effective intervention for individuals living with HIV or living with any chronic condition as its effects diminish after treatment is discontinued. These findings demonstrate the various components that need to be considered when developing and assessing intervention research.

APPENDIX A

A-1. Randomized controlled trials that have used the IMB model to impact ART adherence

Study	Treatment Conditions	Measurements Used	Outcome
1	<p>Enhanced Methadone Maintenance Program (EMMP)- Received 6 months of standard treatment (daily methadone and weekly individual substance abuse counseling and case management) enhanced by the inclusion of a 6-session HIV risk reduction intervention that included (a) an individualized feedback session designed to increase motivation for behavior change, (b) a video demonstration of needle cleaning with bleach and correct use of condoms (c) practice cleaning a needle with bleach and applying condoms to a penis replica, (d) harm reduction negotiation role playing, (e) the provision of harm reduction kits (including needle exchange locations, bleach, alcohol swabs, male and female condoms, and step-by-step instructions), and (f) an emphasis on the importance of sharing harm reduction knowledge and skills with others in their social network</p> <p>HIV_ Harm Reduction Program (HHRP)- Received all components of E-MMP and attended group therapy 2x week. Content matter was comprehensive to address the medical, emotional, and spiritual needs of individuals living with HIV. Group topics included harm reduction skills training; relapse prevention; improving emotional, social, and spiritual health, increasing medication adherence; active participation in</p>	<p>Information – 16-item AIDS Information Sheet (inter item reliability = .72).</p> <p>Motivation – 12-item (measuring confidence in efficacy, intention to use, social norms for use, and perceived difficulty) for each of three harm reduction behaviors: condom use, not sharing needles, and using new or bleach-cleaned needles.</p> <p>Behavioral skills – Demonstrated cleaning a needle with bleach and selecting and applying a latex condom using a penis replica; sessions were videotaped, tapes were rated by research staff blind to treatment assignment (interrater reliability = .98), and the percentage of steps performed correctly was calculated.</p> <p>Adherence – Measured weekly to assess # of missed doses, Adequate adherence was defined as greater than or equal to 95%.</p>	<p>↑ adherence for participants in HHRP than EMMP, $F(1, 67) = 5.67, p = .02$, partial $\eta^2 = .08$.</p> <p>Significantly more patients assigned to HHRP reported $\geq 95\%$ adherence during the treatment phase of the study than patients assigned to E-MMP (OR = 2.74, $p = .04$; CI = 1.03–7.27).</p> <p>Mean values of IMB variables increased for both treatment conditions over time, however only participants who were in the HIV harm reduction program (HHRP) condition demonstrated significantly more improvements in sex-related and drug-related behavioral skills.</p>

	medical care; and making healthy lifestyle choices. Each group session lasted 2 hrs.		
Margolin, A., Avants, S. K., Warburton, L. A., Hawkins, K. A., & Shi, J. (2003). A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. <i>Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association</i> , 22(2), 223–228.			
2	<p>Intervention – Sessions focused on the delivery of factual information and the use of MI techniques to enhance motivation, promote personal responsibility for improving adherence and reducing alcohol use, and develop individualized behavior change plans, received individualized feedback and was provided with a wallet-sized card to facilitate self-monitoring of adherence and drinking behaviors, received tailored skills-building modules, modules included a didactic portion, a self-assessment, skills-building activities, opportunities to practice, and suggested take-home activities, relapse prevention to reinforce skills that had been developed, gain insight about participant experiences, and facilitate access to community based resources.</p> <p>Education – The education condition was matched to the intervention for time and content. Participants attended 8 sessions facilitated by a health educator focused on the provision of factual information through didactic methods and structured discussions about videotapes pertaining to HIV, HAART adherence, and alcohol.</p>	<p>Information, motivation, and behavior skills measures were not reported.</p> <p>Adherence was assessed using a timeline follow-back interview to recall, day by day, all medication doses taken and missed during the past 2 weeks.</p>	<p>↑ percent dose adherence for participants in the intervention condition, $F(1, 107) = 4.0$; $p = 0.05$] and in percent day adherence, $F(1, 111) = 4.1$; $p = 0.05$] compared with participants in the education condition at 3 months but was not sustained at 6 months.</p> <p>On average, percent dose adherence for individuals in the intervention condition increased 14.6% (SD = 26.3%), whereas percent dose adherence for individuals in the education condition increased only 4.3% (SD = 26.5%).</p>
Parsons, J. T., Golub, S. A., Rosof, E., & Holder, C. (2007). Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. <i>Journal of Acquired Immune Deficiency Syndromes (1999)</i> , 46(4), 443–450.			
3	Intervention – Peers individually administered the 6-week mDOT intervention at the Clinic to mDOT	Information, motivation, and behavior skills measures were not reported.	↑ ≥ 90% adherence in mDOT participants than the standard-care

	<p>participants during their morning weekday dose. Evening and weekend doses were not observed. Nighttime and weekend doses were self administered. As part of the daily interaction with participants, peers provided social support, information about the benefits and side effects of HAART, how to address stigma's effect on adherence, and encouragement to participate in community support groups.</p> <p>Standard Care – Includes no-cost medications, clinical and laboratory follow-up, psychosocial adherence support by a trained social worker, and referral to community-based peer support groups. Mandatory pre-HAART counseling involves education about dosing, side effects, nutritional requirements, and the importance of adherence.</p>	<p>Adherence – The percentage of prescribed HAART medication doses taken at 6 and 12 months with the commonly used question “How many of your HIV medication doses did you miss in the last 7 days?” A similar wording with a 30-day assessment period also was included.</p>	<p>participants to achieve at 6 months (7-day measure: 92% mDOT vs. 85%, OR = 2.0, 95% CI: 0.93, 4.5; 30-day measure: 92% mDOT vs. 87%, OR = 1.9, 95% CI: 0.83, 4.3).</p>
<p>Pearson, C. R., Micek, M. A., Simoni, J. M., Hoff, P. D., Matediana, E., Martin, D. P., & Gloyd, S. S. (2007). Randomized control trial of peer-delivered, modified directly observed therapy for HAART in Mozambique. <i>Journal of Acquired Immune Deficiency Syndromes</i> (1999), 46(2), 238–244. http://doi.org/10.1097/QAI.0b013e318153f7ba</p>			
4	<p>Peer Mentoring Intervention – Received sessions 2x/week for 5 weeks, 7 group 2 individual sessions, and 1 “peer volunteer activity” (PVA), during which participants went to a local service organization for 2 to 4 hours to observe, participate, and practice peer mentoring skills. Session topics included: the power of peer mentoring, utilization of HIV primary care and adherence, sex and drug risk behaviors. The final group session focused on review and reinforcement of motivation and skills for behavior change and ended with a graduation ceremony.</p> <p>Video Discussion Intervention –</p>	<p>Information, motivation, and behavior skills measures were not reported.</p> <p>Adherence – Self-report of number of doses of antiretroviral medication prescribed and number of doses missed in the previous day and the previous week. Defined as number of doses taken divided by number of doses prescribed.</p>	<p>Participants in both conditions reported no change in medical care and adherence, and there were no significant differences between conditions.</p>

	Received 8 group sessions with topics related to basic HIV prevention information, watched documentary or self-help videos focused on issues relevant to HIV-positive injection drug users (e.g., prejudice and discrimination, getting a job, incarceration, Red Cross safety tips, overdose prevention), followed by facilitated discussion.		
Purcell, D. W., Latka, M. H., Metsch, L. R., Latkin, C. A., Gómez, C. A., Mizuno, Y., ... INSPIRE Study Team. (2007). Results from a randomized controlled trial of a peer-mentoring intervention to reduce HIV transmission and increase access to care and adherence to HIV medications among HIV-seropositive injection drug users. <i>Journal of Acquired Immune Deficiency</i>			
5	<p>Intervention –</p> <p>Participants found to be less than 95% adherent according to the EDM data were ‘flagged’ for counseling with a clinic physician or nurse. The data were provided to both the subject and his/her clinician as a printout summarizing the percent of doses taken, the percent of doses taken on time, and a visual display of doses taken by time. This process of flagging and counseling was specific to each clinic visit, such that if a subject was counseled in Month 8 but had EDM-measured adherence $\geq 95\%$ at the Month 9 visit, no flagging for counseling occurred. In each counseling session, the clinician reviewed the EDM printout with the subject, explored reasons for missed or off-time doses, and inquired about problems or challenges the subject might be having.</p> <p>Control –</p> <p>In the control arm, subjects continued to provide their EDM data to a study team member at their monthly visits, but these data remained blinded to both subjects and clinicians. However, control subjects whose monthly written self-reports indicated $\leq 95\%$ adherence were also flagged by a</p>	<p>Information, motivation, and behavior skills measures were not reported.</p> <p>Adherence –</p> <p>Measured by EDM and self-report; a visual analog scale (VAS) of proportion of ART medications taken in the previous month; a series of 6 yes/no questions about medication-taking behavior in the previous month (being careless, forgetting, stopping treatment due to feeling better, not taking medications while at work, taking pills early or late, sharing medications); and two quantitative questions on the number of days medications were not taken and number of days medications were taken early or late.</p>	<p>↑ mean adherence in intervention condition than controls at month 12: 96.5 vs. 84.5% (t-test statistic = -3.20; $p = 0.003$)</p>

	<p>study team member for further counseling with a clinician. Thus, subjects in both groups whose adherence in the previous month appeared to be below 95% were identified for counseling, with the difference being the flagging mechanism—EDM for intervention subjects and self-reported adherence for controls. In the counseling sessions with control subjects, which were guided by self reported adherence, the standard of care in China, clinicians were similarly advised to inquire about recent problems that might have affected adherence.</p>		
<p>Sabin, L. L., DeSilva, M. B., Hamer, D. H., Xu, K., Zhang, J., Li, T., ... Gill, C. J. (2010). Using electronic drug monitor feedback to improve adherence to antiretroviral therapy among HIV-positive patients in China. <i>AIDS and Behavior</i>, 14(3), 580–589. http://doi.org/10.1007/s10461-009-9615-1</p>			
6	<p>Participants were randomized to one of three groups: (1) a five-session training intervention that combines cognitive-behavioral components and a 2-week practice trial (enhanced intervention); (2) the same intervention as above but without the practice trial (cognitive-behavioral intervention); or (3) no intervention, but usual clinical care.</p> <p>CBT with Practice Trial – Received education about HIV, ART and the importance of adherence, tailored regimen to daily routine, problem-solving skills to overcome identified adherence barriers, reframing beliefs and attitudes about treatment to increase adherence self-efficacy, and facilitating positive social support for adherence. Received a 2-week, pre-ART placebo practice trial that simulates the challenges of ART adherence, with the exception of treatment side-effects.</p> <p>CBT only – Same as above without Practice</p>	<p>Information, motivation, and behavior skills measures were not reported.</p> <p>Adherence – Measured by EDM and self-report; Participants reported the number of doses taken and missed for each antiretroviral over the previous 3 days</p>	<p>Adherence between the two intervention groups did not differ. Up to week 24, the mean percentage of doses taken by patients of the intervention group remained at 90% or above, compared with nearly 80% in the control group. However, participants in the control group had better adherence at week 48 although this difference was not significant.</p>

	<p>Trial</p> <p>Standard Care – Received education about the importance of adherence and regimen’s dosing instructions; tailored regimen information to daily routine; and was offered a pill box. Follow-up visits were scheduled every 3 months (or more frequently as clinically indicated), and procedures related to adherence typically consisted of inquiries about side effects and whether the patient was taking all prescribed doses.</p>		
<p>Wagner, G. J., Kanouse, D. E., Golinelli, D., Miller, L. G., Daar, E. S., Witt, M. D., ... Haubrich, R. H. (2006). Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578). <i>AIDS (London, England)</i>, 20(9), 1295–1302. http://doi.org/10.1097/01.aids.0000232238.28415.d2</p>			
7	<p>Intervention – Received 4 counseling sessions lasting 2–3 hours each on topics related to disease and markers of clinical progression, practical treatment, nutrition, support, tailoring regimens to lifestyle, managing side effects of medication, developing ways to improve interaction with care staff, methods to address and remove barriers to adherence, create social support conducive to adherence behaviors, use stress management strategies, and to increase self-monitoring and managing adherence lapses.</p> <p>Control – Participated in four 8–12-min video education sessions over a 2-month period. The videos were didactic descriptions of HIV transmission, natural history of the disease and markers of clinical progression, practical treatment issues and questions about nutrition and psychological support. Following the video, participants were able to ask questions of an infectious disease specialist</p>	<p>Information on knowledge and beliefs about AIDS and ART, and psychosocial measures were only measured at baseline by conducting face-to-face interviews</p> <p>Adherence – Self-reported ART adherence was measured and calculated as a percentage of doses taken divided by doses prescribed, using 4-day structured questions (ACTG; Chesney et al. 2000), perfect adherence was considered to be 95% or higher. Pharmacy record adherence estimates were evaluated using drug possession ratios. Drug possession ratios were calculated as the number of days of medication supplied (30 days) divided by the number of days between pharmacy dispensations.</p>	<p>There were no differences in self-reported adherence between participants who were in the intervention group and the control group.</p> <p>No differences were found in adherence measured by pharmacy records and medication possession ratios between groups.</p>

	who had extensive experience in the care and counseling of patients with AIDS.		
Sampaio-Sa, M., Page-Shafer, K., Bangsberg, D. R., Evans, J., Dourado, M. de L., Teixeira, C., ... Brites, C. (2008). 100% adherence study: educational workshops vs. video sessions to improve adherence among ART-naïve patients in Salvador, Brazil. <i>AIDS and Behavior</i> , 12(4 Suppl), S54–62. http://doi.org/10.1007/s10461-008-9414-0			

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VITA

Sofie Ling Champassak was born on October 10, 1986, in San Diego, California. She attended local public schools and graduated from Mira Mesa High School in 2004. She attended San Diego City Community College and then transferred to San Diego State University (SDSU) where she graduated, Phi Beta Kappa and magna cum laude, in 2010. Her degree was a Bachelor of Arts degree in Psychology. She was a member of the McNair Scholars Program and the NIMH funded Career Opportunities in Research Scholars Program.

Sofie started her doctoral training in Clinical Health Psychology at the University of Missouri-Kansas City (UMKC) in the fall of 2010. She has been involved in research with Project MOTIV8, an NIMH funded 3-arm randomized control trial testing the efficacy of novel approaches to improve antiretroviral medication adherence in people with HIV. She has also assisted in research with KC Quest, an NIH funded 3-arm randomized control trial to assess different types of communication with smokers. KC Quest is dedicated to learning from smokers who do not want to quit, or are not ready to quit, and how health care providers communicate with them. Sofie has completed and collaborated on multiple research projects that have been presented in national and international research conferences. She has received awards from the UMKC Women's Council, the UMKC School of Graduate Studies, and the National Cancer Institute to present at research conferences. She has authored and co-authored multiple peer-reviewed manuscripts published in the *Journal of Evaluation and Clinical Practice*, *Pediatric Emergency Care*, among other journals.

Sofie received clinical training at the Kansas City Care Health Clinic, Leavenworth Veteran's Affairs Medical Center, Shawnee Mission Medical Center, Children's Mercy Hospital, and the Kansas City Center for Anxiety Treatment. Sofie will complete an APA Accredited Psychology internship at the Veteran's Affairs Sepulveda Ambulatory Care Center in Los Angeles, California. She is a member of the Society of Behavioral Medicine and the Motivational Interviewing Network of Trainers.