# INVESTIGATING THE INTERRELATIONSHIPS BETWEEN FATIGUE, MEMORY IMPAIRMENT, AND MEDICATION ADHERENCE AMONG PERSONS LIVING WITH HIV DISEASE

_____

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

_____

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

_____

By

Marika P. Faytell

May, 2017

INVESTIGATING THE INTERRELATIONSHIPS BETWEEN FATIGUE, MEMORY IMPAIRMENT, AND MEDICATION ADHERENCE AMONG PERSONS LIVING WITH HIV DISEASE

_____
Marika P. Faytell

**APPROVED:**

_____
Steven P. Woods, Psy.D.
Committee Chair

_____
Paul Massman, Ph.D.

_____
Clayton Neighbors, Ph.D.

_____
Rustin D. Crutchley, Pharm.D.

_____
Antonio D. Tillis, Ph.D.
Dean, College of Liberal Arts and Social Sciences
Department of Hispanic Studies

# INVESTIGATING THE INTERRELATIONSHIPS BETWEEN FATIGUE, MEMORY IMPAIRMENT, AND MEDICATION ADHERENCE AMONG PERSONS LIVING WITH HIV DISEASE

_____

An Abstract of a Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

_____

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

_____

By

Marika P. Faytell

May, 2017

**ABSTRACT**

Fatigue and memory impairment are each highly prevalent in HIV disease (e.g., Heaton et al., 2011; Jong et al., 2010), and exert independent influences on adherence to antiretroviral therapy. However, the combined effects of fatigue and memory impairments on adherence, as well as possible modulating factors of these effects, remain unknown. This study adopted the Aaronson et al. (1999) model of fatigue, which predicts that fatigue depletes compensatory resources, thus leaving HIV+ individuals vulnerable to the impact of memory impairment on adherence. The first aim was to determine the best-fitting model of the relationships between fatigue, compensatory strategy use, retrospective and prospective memory, and adherence. The second aim was to assess whether changes in fatigue, strategy use, and memory were associated with changes in perceived medication management efficacy over one year. Study participants included 177 HIV+ persons who completed a semi-structured clinical interview, comprehensive neurocognitive battery, a series of questionnaires, and a physical evaluation. cART adherence was obtained behaviorally with MEMS caps and by self-report of medication management. Readministration of these assessments (except for the MEMS) was conducted with 57 participants at follow-up about one year later. Structural equation modeling revealed that adherence was most parsimoniously represented by contributions from measures of perceived medication management efficacy and MEMS. In the first aim, the data were fit best by a model comprised of direct and covarying negative effects of fatigue and strategy use on adherence, which were independent from a direct positive effect of prospective memory (controlled for retrospective memory) on adherence. In the second aim, data were fit best by a model comprised of changes in fatigue and strategy use, but not prospective memory, as significant covariates of change in perceived medication management efficacy. These data revealed dynamic interplay between fatigue, strategy use, and perceived efficacy, with separate and stable contributions of prospective memory to perceived efficacy. These and prior findings are discussed in the context of metacognitive awareness. Ultimately, enhanced understanding of these relationships provides valuable clinical information that can inform efforts to (1) improve patient-specific targeting of fatigue-

related assessments and interventions; and (2) develop effective interventions for bolstering adherence in seropositive populations.

**ACKNOWLEDGEMENTS**

This dissertation would not exist without the support and encouragement of many, many people. First, I would like to thank my committee for their time, energy, and invaluable suggestions. Together, you helped me shape my ambitious ideas into specific and meaningful research questions. I would like to extend a particular thank you to Dr. Clayton Neighbors for his significant contributions to the design and execution of my statistical analysis; without his guidance, this project would address much less sophisticated questions.

I would like to express my deep gratitude to my mentor, Dr. Steven Woods. Thank you for taking on a new advanced student in the middle of the year, while you were in the process of building a lab from scratch. Thank you for the many, many hours you have invested in meeting with me, providing multitudinous edits of my work, and replying to my frantic emails. Thank you for teaching me how to be an effective writer and researcher. Most of all, thank you for showing me how to cultivate a productive and supportive lab environment. Being a member of your lab has been a joy, and I will miss it dearly.

I would also like to thank my fellow CNDL lab members David Sheppard, Gunes Avci, Vickie Kordovski, and Savanna Tierney, for helping me solve the myriad practical problems I encountered as a new lab member. Thank you also for being so forgiving of my chronic fourth-year busyness, and for providing unwavering support and encouragement throughout my time in the lab. Your presence and support made the dissertation process inexpressibly more enjoyable.

Finally, I would like to thank my family for accompanying me on this crazy ride known as graduate school. To my fellow Neuronauts Elyssa Gerst, Alex Alverson, and Lee Wiegand: thank you for being there for me every step of the way. To the rest of my Houston family: thank you for providing me with a lifetime's worth of friendship, fun, food, and frisbee in four short years. To my parents, Dani Pers and David Faytell: thank you for your unwavering confidence in my abilities, and your willingness to traverse the long miles between Texas and Massachusetts many times over. And to my fiancé, Derek Grimm: this is for you. Thank you for everything.

**TABLE OF CONTENTS**

## LIST OF TABLES AND FIGURES

Investigating the Interrelationships between Fatigue, Memory Impairment, and Medication Adherence among Persons Living with HIV Disease

## INTRODUCTION

Human immunodeficiency virus (HIV) is a chronic, lifelong disease that constitutes a very real public health concern. According to the Centers for Disease Control and Prevention (CDC), over 40,000 new cases are reported every year in the United States alone. As of 2013, an estimated 1.2 million people in the United States are living with HIV disease (CDC, 2015a). HIV is a lentivirus that targets immunoreactive cells, including helper T cells ($CD4^+$ T cells in particular), macrophages, and dendritic cells. HIV infection of these cell types causes direct viral killing of infected cells; pyroptosis of abortively infected helper T cells; death of infected CD4 cells by cytotoxic lymphocytes; and apoptosis of uninfected bystander cells. Together, these mechanisms contribute to the decline of CD4 cell counts. Once CD4 cell counts drop below a critical level (e.g., 200 c/ml), the host loses cell-mediated immunity and becomes significantly more susceptible to opportunistic infections (e.g., cryptococcal meningitis, toxoplasmosis, Karposi's sarcoma, etc.). These symptoms of infection are collectively referred to as acquired immune deficiency syndrome (AIDS).

While eradication of HIV DNA has not been achieved, medical advances have permitted the control of HIV RNA replication. Over the past decade, prognosis and clinical implications of HIV have improved significantly with advances in pharmacotherapy, specifically the advent of combination antiretroviral therapies (cART; also known as highly active antiretroviral therapy, or HAART). cART is comprised of multiple classes of antiretroviral agents that act in concert on various stages of the HIV life cycle to suppress plasma HIV RNA (i.e., viral load; DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS), 2016), reverse immunologic decline (e.g., Ryscavage et al., 2014), reduce progression of HIV disease, and decrease mortality (e.g., Bhaskaran et al., 2008).

Notably, cART is so successful in controlling HIV infection that HIV is now considered a chronic, manageable condition in many areas of the world (DHHS, 2016). In the United States and in other developed countries, survival rates following HIV infection have improved significantly since the introduction of cART in 1996 (e.g., Powderly 2002), even compared to rates associated with monotherapy or bi-therapy regimens (de Olalla et al., 2002). The average lifespan for individuals living with HIV has increased to over 70 years old on average, very close to that of seronegative North Americans (Samji et al., 2013).

Successful management of HIV disease via cART is predicated on a series of stages. Collectively known as the HIV treatment cascade, the stages are: (1) knowledge of HIV status through diagnostic testing; (2) engagement in consistent HIV-related health care; and (3) receipt of and adherence to effective cART regimens. Successful progression through the first three stages ultimately results in a fourth stage, which is (4) continual suppression of viral loads below detectable levels. Achievement and maintenance of viral load suppression are the primary goals of cART. Suppression precludes the virus from replicating quickly enough to develop resistance to the medications (Deeks et al., 1997) and lowers rates of transmission (Cohen et al., 2011).

Current treatment guidelines define optimal viral suppression as viral load maintained below the level of detection (DHHS, 2016). Detection threshold depends on the assay used, but generally ranges between <20 and 75 HIV RNA copies/ml. Consistent with these guidelines, most studies set viral suppression thresholds at <50 copies/mL (e.g., Mitchell et al., 2015). Conversely, outright virologic failure is defined as a confirmed viral load >200 copies/ml (i.e., two or more consecutive readings of viral load > 200 copies/ml; DHHS, 2016). This measurement discrepancy accounts for the common and well-documented existence of transient viral blips, which occur when viral load transiently increases above detectable thresholds, but are immediately preceded and followed by viral loads below detectable levels (DHHS, 2016; Young et al., 2015). Thus, defining virologic failure with a threshold of >200 copies/ml is thought to eliminate most cases of viral blips, as well as to control for assay variability (DHHS, 2016).

Despite the evolution of health care systems in response to the HIV epidemic (Holmes & Sanne, 2015), rates of attrition are high at each stage of the treatment cascade. According to recent estimates, only 87 percent of HIV+ individuals in the United States know their serostatus (CDC, 2015b). Among the estimated 942,000 individuals in the United States who were aware of their HIV diagnosis in 2010, about 77 percent were linked to HIV-related health care, and only 51 percent were retained in care (CDC, 2011). Among those receiving care, 89 percent were prescribed ART regimens, and 77 percent of those prescribed ART maintained viral loads below 200 copies/ml. Cumulatively, only 28 percent of all HIV-infected individuals in the United States maintain viral loads below 200 copies/ml (CDC, 2011). These estimates underscore the significant gaps still present in the treatment cascade (i.e., late HIV diagnosis, insufficient rates of ART prescription, and suboptimal adherence to ART regimens) that represent significant barriers to reaching optimal treatment outcomes and ultimately halting the progression of the HIV epidemic (Gardner et al., 2011).

Among seropositive individuals receiving cART, suboptimal adherence represents the primary barrier to reaching optimal treatment outcomes. Adherence is defined as the extent to which medication-taking behaviors match recommendations made by healthcare providers. Consistently high cART adherence is necessary to achieve and maintain viral suppression. Adherence is also strongly associated with decreased risk of virologic failure (e.g., Gordon et al., 2015), lower rates of treatment-resistant viral strains (e.g., Harrigan et al., 2005) and lower mortality rates (e.g., de Olalla et al., 2002; Lima et al., 2007). Adherence may also be linked to occurrence of viral blips, as indicated by some (Podsadecki et al., 2007; Raboud et al., 2002), but not all (e.g., Miller et al., 2004) studies. In contrast, suboptimal cART adherence is associated with poor health-related outcomes, including greater risk of incomplete viral suppression (Catz et al., 2000), development of viral resistance (Bangsberg, Kroetz, & Deeks, 2007; Harrigan et al., 2005), and disease progression (Bangsberg et al., 2001). Thus, identifying salient risk factors for nonadherence and developing targeted interventions are paramount for improving HIV prognosis.

Historically, optimal adherence was defined as taking over 90 percent of prescribed doses (e.g., de Olalla et al., 2002; Woods et al., 2009a). However, advances in cART regimen complexity over the past 20 years provide higher rates of viral suppression and lower risk of virologic failure at lower rates of adherence. In one recent study, viral suppression was achieved for more than 80 percent of HIV+ individuals with adherence rates between 80 and 84 percent; furthermore, the odds ratio of viral suppression at 80 percent adherence was not significantly different from the odds of suppression at 95 percent or greater (Viswanathan et al., 2015). Similarly, in a study comparing three different cART regimens, adherence rates between 80 and 90 percent were associated with no more than 3.5 percent virologic failure rate, compared to 1.1 percent virologic failure rate for adherence rates of 90 percent or greater (Gordon et al., 2015).

Nevertheless, a significant proportion of seropositive adults receiving cART continues to report suboptimal adherence; across three recent studies, 47 to 61 percent of participants reported < 95 percent adherence (Biswas et al., 2014; Sax et al., 2012; Viswanathan et al., 2015). In another study, 29 percent of participants reported < 90 percent adherence, and 18 percent of participants reported < 80 percent adherence (Gordon et al., 2015). A third study noted that 47 percent of participants reported adherence rates below 95 percent, and 90 percent of them did not achieve viral suppression (Biswas et al., 2014). In other recent studies, average rates of adherence were below 90 percent (e.g., Andrade et al., 2013; Pellowski & Kalichman, 2015).

Furthermore, adherence is affected by myriad health-related factors, including health literacy (e.g., Kalichman, Ramachandran, & Catz 1999), diet and exercise (e.g., Pellowski & Kalichman, 2015), beliefs about health and medication (e.g., Kalichman, Kalichman, & Cherry, 2015), demographics (e.g., Duran et al., 2001), social support (e.g., Mitchell et al., 2015), and age (e.g., Barclay et al., 2007) among others. Poor adherence has been found to be twice as high for younger participants than for older participants (e.g., 68 percent vs. 33 percent; Barclay et al., 2007). Rates of non-adherence are higher when neuropsychiatric symptoms are present, particularly depression (e.g., Gonzalez et al., 2011) or substance use (e.g., Hinkin et al., 2007). Efforts to improve rates of adherence have largely produced modest or

short-term results (e.g., Binford, Kahana, & Altice, 2012; Nachega et al., 2014), with relatively greater improvements associated with treatments that target secondary barriers to adherence, such as depressive symptomatology (e.g., Sin & Matteo, 2014).

**Focus of the Current Study**

In this study, we sought to further develop our understanding of the complex predictors and moderators of adherence behavior to inform treatment. To do so, we took a theory-driven approach to examine the interplay of HIV-associated memory impairment and fatigue, two clinically significant factors in cART adherence. Neurocognitive impairment is highly prevalent in HIV disease; approximately 30 to 50 percent of seropositive adults evidence clinically apparent signs or symptoms of neurocognitive impairment (Heaton et al., 2011). Although no unified neurocognitive profile has been observed across individuals who meet criteria for HIV-associated neurocognitive disorders (HNRC Group et al., 2008), patterns of impairment consistent with subcortical or frontostriatal brain systems dysfunction are often apparent, with executive functions and memory domains most commonly affected (Heaton et al., 2011). Indeed, impairments in learning and memory are hallmarks of HIV-associated neurocognitive disorders in the cART era. Unlike the incidence of impairments in motor functioning, cognitive speed, and verbal fluency, which has declined since the advent of cART, memory impairments are still common among seropositive individuals taking effective cART (Heaton et al., 2011). Memory resources are intuitively necessary for executing adherence behaviors, such as recalling the correct dosage (i.e., retrospective memory) or remembering to take a dose at a specific time (i.e., prospective memory); unsurprisingly, robust relationships are observed between adherence and impairments in retrospective (e.g., Hinkin et al., 2004) and prospective (e.g. Woods et al., 2009a) memory. Among physical symptoms, fatigue is the most common constitutional symptom reported by individuals with HIV (Blackstone, Moore, & Woods, 2013), and is a common side effect of many antiretroviral medications (e.g., DeJesus et al., 2004), including integrase strand transfer inhibitors (INSTIs), which are part of first line treatment regimens (DHHS, 2016). Early data show that fatigue is associated with worse cART adherence (e.g., Johnson et al., 2005; Trotta et al., 2003). However, the role of fatigue in cART adherence for individuals with HIV-associated

memory impairments remains unelucidated. Presented here is a review of the relevant literature, with emphases on HIV-associated profiles of neuropathogenesis, general neurocognitive impairment, retrospective and prospective memory impairments, and fatigue, followed by investigation of these relationships using path analysis in a retrospective study of previously collected data.

**Neuropathogenesis of HIV Disease**

HIV infection commonly results in central nervous system (CNS) diseases through two pathways. Uncontrolled HIV infection causes progressive immune deficiency, of which opportunistic pathogens can take advantage, thus resulting in CNS diseases secondary to HIV infection (see Ellis, Calero, & Stockin, 2009 for a review). Alternately, HIV can infect CNS tissue directly, causing HIV-specific neurological syndromes. As the former mechanism has become increasingly uncommon in the cART era (e.g., Neuenburg et al., 2002), research efforts have shifted to focus on the latter mechanism, characterized as primary HIV-induced CNS disease (e.g., Ances and Ellis, 2007). Autopsies of HIV-infected individuals revealed that the brain was the second most frequently infected organ after the lungs (Masliah, DeTeresa, Mallory, & Hansen, 2000). Entry into the CNS occurs through a "Trojan Horse" mechanism, involving infected macrophage-monocyte cells that cross the blood-brain barrier (for review, see Ances & Ellis, 2007). While HIV does not infect neurons directly, HIV-1 DNA has been detected in astrocytes, neuroendothelial cells, and microglial cells (An et al., 1999).

Viral neuropenetration occurs early in the disease progression. In one recent study, 10 to 25 percent of participants evidenced either local viral replication in the CNS or a robust inflammatory response in CSF fluid within the first two years of infection; in about 16 percent of participants, CNS involvement persisted over time (Sturdevant et al., 2015). HIV is thought to target CNS tissue because microglia and other neural cells present there express the primary cytokine receptors and co-receptors necessary for HIV to enter cells (Hult, Chana, Masliah, & Everall, 2008). The majority of viral replication in CNS tissue occurs in microglia and monocyte derived macrophages; immune activation of these cells, along with that of astrocytes, is thought to be the most significant cause of neurotoxicity in the CNS (McArthur, Brew, & Nath, 2005; Watkins & Treisman, 2015). HIV viral proteins also induce indirect

neurotoxic effects on neurons and glia, including synaptodendritic injury (Bellizzi, Lu, & Gelbard, 2006) and dendritic simplification (Masliah et al., 1997), with striatal dopaminergic neurons demonstrating particular susceptibility (for a review, see McIntosh, Rosselli, Uddin, & Antoni, 2015).

While HIV-associated neuropathologies have been observed throughout the CNS (Di Stefano, Sabri, & Chiodi 2005), HIV is known to preferentially attack fronto-striato-thalamocortical white matter tracts (Ellis, Calero & Stockin, 2009), as well as the basal ganglia (Hinkin et al., 1995). HIV also affects the structure and function of other white matter tracts and neural systems, including the parietal lobes (Hinkin et al., 1995) and corpus callosum (Wu et al., 2006). HIV status has also been associated with gray matter volume loss in the posterior and inferior temporal lobes, the parietal lobes, and the cerebellum (Becker et al., 2012). Regional differences in susceptibility to injury from HIV infection appear to be due in part to unique neurotoxic and transport properties of viral proteins like Tat and other viral proteins (e.g., Bruce-Keller et al., 2003; for a review, see Rumbaugh & Nath, 2006).

Given the practical and ethical difficulties inherent in examining HIV-related neuropathologies among samples of living seropositive persons, investigations are primarily limited to autopsy case studies or non-invasive procedures, such as PET scans (e.g., Hinkin et al., 1995) or CSF samples (e.g., Sturdevant et al., 2015). Alternately, many researchers study HIV-related neurological impairment indirectly by investigating the incidence, prevalence, and nature of HIV-associated neurocognitive disorders, which are known correlates of primary HIV-induced CNS disease (e.g., Anthony & Bell, 2008; Clifford & Ances, 2013).

**HIV-Associated Neurocognitive Disorders (HAND)**

While impairments in neuropsychological functioning are not observed in all persons with HIV disease, clinically apparent signs and symptoms of mild or greater neurocognitive impairment are present in about 36 percent of individuals with asymptomatic HIV infection, and in at least 45 percent of persons who have developed AIDS (Heaton et al., 2011). HIV-associated neurocognitive impairments are not represented by a unitary neurocognitive profile (e.g., Dawes et al., 2008); rather, they have come to be described by a collection of deficits, defined as HIV-associated neurocognitive disorders (HAND).

Current estimates of the annual incidence rate of HAND over the lifespan are between 15 and 20 percent (Robertson et al., 2007; Sheppard et al., 2015). Presence of HAND is associated with worse health-related outcomes, including lower health literacy (Morgan et al., 2015), poorer medication management (e.g., Thames et al., 2011), declines in activities of daily functioning (for a review, see Gorman et al., 2009) and greater risk of poor retention in HIV care (Jacks et al., 2015).

Unlike other neurodegenerative diseases (e.g., Alzheimer's disease), HAND is not invariably progressive (Woods et al., 2009b). A sizeable proportion of seropositive individuals demonstrate a fluctuating course of neurocognitive functioning over time, and improvement of symptoms to baseline neurocognitive function is possible (Antinori et al., 2007). Robertson et al. (2007) analyzed the neurocognitive data of 991 HIV+ individuals in 14 prospective randomized cART clinical trials who were assessed at baseline and again up to 48 weeks later. Among participants with baseline neurocognitive impairment, 44 percent improved at follow-up, and 56 evidenced stable neurocognitive impairment. Among participants with normal neurocognition at baseline, 21 percent evidenced incident neurocognitive impairment at follow-up. Recently, Vassallo et al. (2014) assessed neurocognitive functioning of 96 seropositive adults over two years. At follow-up, 6 percent of participants improved, 39 percent worsened, and 58 percent exhibited stable neurocognitive functioning. Finally, in a sample of 436 seropositive adults assessed repeatedly over one to six years, 16 percent of participants demonstrated improved neurocognitive performance, while 23 percent evidenced declines and 61 percent remained stable (Heaton et al., 2015).

The current nosology of HAND is based on recommendations from an NIH working group (Antinori et al., 2007), and is comprised of three possible diagnoses: (1) asymptomatic neurocognitive impairment (ANI); (2) HIV-associated mild neurocognitive disorder (MND); and (3) HIV-associated dementia (HAD). HAND diagnoses are determined through assessment of at least five neurocognitive domains known to be impacted by HIV infection. Domains include attention/working memory, speed of information processing, language, motor skills, executive functions, sensory perceptual abilities, and episodic memory. Ideally, assessments are conducted using performance-based neurocognitive batteries

and interpreted with demographically-appropriate normative data (Woods et al., 2009b), though utilization of mental status exams is permitted in settings with limited resources (Antinori et al., 2007). HAND is not diagnosed when neurocognitive impairment can be solely attributed to delirium or a comorbid condition like psychosis or active substance use disorders. Specific HAND diagnoses are determined by the severity of neurocognitive impairment and the presence or absence of declines in daily functioning (e.g., producing more errors at work, difficulty managing finances, etc.).

According to the Frascati criteria (Antinori et al., 2007), ANI is the mildest and most common form of HAND. ANI is thought to account for the majority of cases of HAND. In a sample of 1,555 HIV+ adults recruited from six university clinics from across the United States, 33 percent met criteria for ANI, 12 percent met criteria for MND, and only two percent met criteria for HAD (Heaton et al., 2010). Criteria for ANI include demographically-adjusted normative scores greater than one standard deviation below the mean in at least two cognitive domains (Antinori et al., 2007). Diagnosis of ANI does not require observed declines in daily functioning.

The diagnostic criteria for ANI are considered too liberal by some research groups, who argue that the criteria produce unacceptably high false positive rates, and raise ethical dilemmas. Gisslen, Price, and Nilsson (2011) noted that application of these criteria results in ANI diagnosis for 16 to 21 percent of seropositive individuals with effective cART. Assuming normal distribution, about 16 percent of any population is expected to score more than one standard deviation below the mean on a single neuropsychological test. Expanding to multiple tests, Gisslen, Price, and Nilsson (2011) reported an 18 to 21 percent probability of scoring more than one standard deviation below the mean in one test (or average of tests) per domain in at least two of five domains tested. Furthermore, the probability of an abnormal score would increase as number of domains tested increased. Similarly, Meyer, Boscardin, Kwasa, and Price (2013) reported false-positive frequencies of two to 74 percent for ANI and MND, compared to a zero to eight percent false-positive frequencies for HAD. Gisslen, Price, and Nilsson (2011) also raised ethical concerns about diagnosing people with neurocognitive impairments in the absence of symptoms or complaints; given the uncertain relevance of ANI, the diagnosis may cause unnecessary anxiety and

impact employment without cause. However, ANI diagnosis has been associated with a two- to six-fold greater risk of declines in daily functioning, which are the hallmarks of MND and HAD (Grant et al., 2014), suggesting that ANI diagnosis is relevant for predicting later daily functioning. Additionally, many individuals with ANI lack awareness of deficits in functional performance (Chiao et al., 2013), suggesting that reliance on self-report for assessment of daily functioning may underestimate the prevalence of symptomatic impairment among HIV+ individuals currently diagnosed with ANI.

Approximately 30 to 50 percent of individuals diagnosed with HAND demonstrate some level of impairment in daily functioning, and about 20 to 40 percent of HAND diagnoses meet criteria for MND (Woods et al., 2009b). MND diagnosis comprises five to 20 percent of the overall HIV+ population (Woods et al., 2009b). MND is diagnosed by the presence of mild-to-moderate neurocognitive impairment, defined as greater than one standard deviation below the mean on demographically-adjusted normative scores in at least two cognitive domains, accompanied by mild declines in daily functioning (Antinori et al., 2007). Mild interference in daily functioning is observed when at least two of the following criteria are met: (1) declines in two or more instrumental activities of daily living (e.g., financial management); (2) significant reduction in job responsibilities or unemployment, secondary to decline in neurocognitive abilities; (3) reduced vocational functioning (e.g., more errors, lower productivity, or more effort needed to meet the same level of productivity); (4) more difficulty in two or more cognitive ability areas in daily functioning; and (5) performance greater than one standard deviation below the mean on a performance-based laboratory measure of daily functioning (e.g., a medication management task) (Woods et al., 2009b).

HAD is the most severe form of HAND. While the incidence and prevalence of the milder forms of HAND have remained stable in the era of cART (Heaton et al., 2010), even increasing among medically asymptomatic HIV+ individuals (Heaton et al., 2011), the incidence of HAD has dropped significantly (e.g., Ances & Ellis, 2007; Sacktor et al., 2001). Presently, about five percent of individuals with HAND, and approximately 1 percent of the HIV population overall, meet criteria for HAD (Heaton et al., 2010). HAD is diagnosed by the presence of moderate-to-severe cognitive impairment, defined by

scores that are two or more standard deviations below demographically-adjusted normative means in at least two cognitive domains, as well as marked declines in daily functioning that cannot be fully attributed to comorbid conditions or delirium (Antinori et al., 2007). Regarding the functional impairment criterion, HAD diagnosis requires evidence of two or more of the following: (1) unemployment due to cognitive impairment; (2) dependence on others for two or more instrumental activities of daily living due to cognitive impairment; (3) evidence of declines in four or more cognitive ability areas related to daily functioning; and (4) scores two or more standard deviations below the mean on a performance-based laboratory measure of daily functioning, or greater than one standard deviation below the mean on two laboratory measures of functioning (Woods et al., 2009b).

**Disease Correlates of HAND**

Incidence and severity of HAND are sometimes related to physiological markers of HIV disease. Neurocognitive impairment is predicted by low nadir CD4, and is commonly associated with AIDS diagnosis (Heaton et al., 2010). Severity of neurocognitive impairment has also been associated with concurrent plasma CD4+ lymphocyte counts and level of HIV RNA in the dorsolateral prefrontal cortex collected about six months after neuropsychological testing (Gelman et al., 2013). Elevated levels of plasma sCD163, a monocyte/macrophage activation marker, have been observed in individuals with MND but not ANI or cognitively intact individuals, and remained elevated among individuals evidencing stable neurocognitive impairment (Burdo et al., 2013).

**HIV-Associated Episodic Memory Impairments**

Episodic memory impairments are prevalent in HIV disease, with estimates ranging between 40 and 60 percent (e.g., Heaton et al., 1995; Rippeth et al., 2004). Level of episodic memory impairments is typically mild to moderate, but can become more severe as HIV disease advances (e.g., Reger et al., 2002). HIV-associated memory deficits are observable across a range of modalities (e.g., visual vs. verbal) and task parameters (e.g., list learning vs. story recall; simple vs. complex) (see Woods et al., 2009b for a review), suggesting generalized memory impairments. However, episodic memory comprises a number of related but dissociable neuropsychological constructs, and HIV disease does not uniformly

affect all types of episodic memory. Compared to other constructs, the prevalence of HIV-associated impairments in retrospective and prospective memory is relatively high, and their presence and severity confer greater risk of impairment in functional domains, particularly adherence.

### *Retrospective Memory*

#### *Prevalence and Profile*

Retrospective memory (RM) refers to long-term storage of newly learned information coupled with the ability to later retrieve stored information in response to explicit internal or external cues. Thus, deficits in RM reflect depletion of cognitive resources necessary for self-directed storage and retrieval of information. HIV-associated RM deficits are observed most consistently in the context of a mixed encoding and retrieval profile. Mixed encoding and retrieval is the most commonly observed profile of memory deficits among HIV+ individuals, with approximately 30 to 40 percent reflecting this pattern (e.g, Becker et al., 1995), though significant variability is observed between individuals (Murji et al., 2003). This profile is characterized by impairments in both immediate free recall and RM in the context of relatively better recognition (Woods et al., 2005). RM impairments in the context of rapid forgetting profiles are observed much less frequently, primarily among individuals with HAD (Scott et al., 2006). Additionally, rapid forgetting in the context of HAD is thought to reflect shallow encoding rather than pure RM impairment, as indicated by accompanying elevations in recency effects (Scott et al., 2006).

HIV-associated RM deficits are often associated with decreased employment of strategic organizational strategies, like semantic clustering (e.g., Peavy et al., 1994), which decrease further as severity of HAND increases (Gongvatana et al., 2007). Limited free recall, inconsistent recall across learning trials, interference effects, and elevated rates of repetition errors have also been observed (e.g., Delis et al., 1995; Peavy et al., 1994), while consolidation and recognition discrimination are less commonly impaired (e.g., Delis et al., 1995).

#### *Disease Correlates*

At the neural systems level, the mixed encoding and retrieval profile is most consistent with frontostriatal loop pathogenesis (Castelo et al., 2006), a hallmark of HIV-associated neuropathology.

Worse RM performance is significantly associated with decreased levels of interferon gamma-soluble cytokine and interleukin-8, and increased levels of interleukin-18 (Correia et al., 2013). One longitudinal analysis observed an association between improvements in RM performance and higher CD4 cell count (Fama et al., 2009).

*Functional Impact*

RM performance is strongly correlated with several daily functioning domains, including employment, medication management, and social planning. RM is associated with employment status (van Gorp et al., 1999), and is a strong predictor of re-attaining employment after being unemployed (van Gorp et al., 2007). In a study of work persistence (i.e., maintenance of newly obtained employment), participants with general neurocognitive impairment were less likely to achieve persistent employment, a relationship that appeared to be driven by RM performance (van Gorp et al., 2008). RM is strongly correlated with performance on laboratory-based medication management tasks (e.g., Albert et al., 1999; Hinkin et al., 2004), with poorer RM associated with worse medication management. In one study, poor RM at baseline was associated with incident declines in medication management performance a year later (Thames et al., 2013). RM is also associated with self-reported performance on social planning and everyday memory tasks (Benedict, Mezhir, Walsh, & Hewitt, 2000).

***Prospective Memory***

*Prevalence and Profile*

Failures of prospective memory (PM) are common among individuals with HIV; seropositive individuals endorse more complaints of PM failures in their daily lives than seronegative counterparts (Woods et al., 2007a), and demonstrate mild-to-moderate impairments on performance-based measures of PM (Carey et al., 2006; Martin et al., 2007). PM, or "remembering to remember," refers to the ability to recall and execute intended actions in response to predetermined cues encountered after a delay. PM differs from and is dissociable from RM in that PM is a complex cognitive process that relies heavily on multiple neurocognitive processes, only one of which is RM. Specifically, PM is a complex cognitive process in which an intention (e.g., I will take my medication when the alarm rings) is paired with a

specific cue (e.g., the ringing alarm). PM cues can be time-based (e.g., taking medication at 2 pm) or event-based (e.g., taking medication when an alarm rings). Once the pairing is encoded, individuals must monitor their environment for the target cue, while simultaneously engaging in an ongoing activity that precludes overt rehearsal (e.g., normal daily activities). After encountering the target cue, the intended action must be retrieved from RM and executed properly (Kliegel et al., 2008).

Execution of PM tasks relies heavily on multiple neurocognitive processes. Proper encoding of the cue-intention pairing requires learning and attention, while retention and recall of the intended action relies on RM. A number of different executive functions are important as well (e.g., the ability to switch between monitoring the environment and executing the ongoing task). Unsurprisingly, HIV-associated PM deficits are associated with impaired RM and executive dysfunction (e.g., Carey et al., 2006); however, evidence from cognitive (Gupta et al., 2010), biomarker (Woods et al., 2006), and daily functioning (Woods et al., 2008a) studies support PM as dissociable from RM and other neuropsychological constructs. In other words, RM contributes necessary component resources to PM, but intact RM is not sufficient for intact PM.

PM can be further characterized by the nature of processing demands necessary to complete specific PM tasks. According to the Multiprocess Theory of PM (Einstein & McDaniel, 2005), each aspect of PM (e.g., encoding of the cue, intention, and cue-intention pairing; monitoring of environment; cue detection; and retrieval of paired intention) places demands on the available pool of cognitive resources to variable extents. Variation occurs on a continuum from low (i.e., spontaneous/automatic) to high (i.e., strategic/executive) demand. For example, time-based PM tasks tend to require strategic monitoring resources to independently disengage from the ongoing task to periodically check the clock. Conversely, event-based PM tasks typically rely on external, salient cues and require more spontaneous processes.

HIV-associated PM deficits tend to reflect greater dysregulation in the strategic processes of intention encoding and retrieval. For example, HIV+ individuals evidence impairments in strategic time monitoring (i.e., clock checks) during time-based PM tasks (Doyle et al. 2013) and tend to demonstrate

larger effect sizes for time- versus event-based PM deficits (Martin et al. 2007; Zogg et al. 2011). Furthermore, interventions designed to support strategic processing have been shown to improve PM among young adults with HIV (Loft et al., 2014; Woods et al., 2014).

*Disease Correlates*

PM is highly dependent on frontal systems (e.g., Brodmann's area 10; Woods et al., 2009b), particularly prefronto-striatal circuits (e.g., Carey et al., 2006). In one study, HIV+ participants with poor PM exhibited significantly decreased fractional anisotrophy in the superior corona radiata, the corpus callosum, and the cingulum, compared to HIV+ participants with intact PM (Hoare et al., 2012). PM deficits have been associated with elevations of some HIV biomarkers of macrophage activation and neuronal injury, including plasma monocyte chemoattractant protein-1 (MCP-1), cerebral spinal fluid (CSF) soluble receptor for tumor necrosis factor type II, and CSF tau; these biomarker levels were not similarly associated with RM deficits (Woods et al., 2006).

*Functional Impact*

Like RM, PM is associated with employment status (e.g., Woods et al., 2011), and medication management (e.g., Woods et al., 2008b). PM deficits are also associated with greater dependence upon others for completing instrumental activities of daily living (IADLs; e.g., financial management, grocery shopping, cART adherence, housekeeping, and employment). In one study, PM accounted for a significant percent of the variance in summed total severity of declines in IADL functioning above that explained by RM and current affective distress (Woods et al., 2008a).

***Memory and cART Adherence***

*Retrospective Memory*

RM deficits are significantly associated with cART non-adherence (e.g., Ettenhofer et al., 2010; Hinkin et al., 2004). One study reported that presence of RM dysfunction conferred a greater than twofold risk of poor cART adherence (OR: 2.25; Hinkin et al., 2002). In another study, non-adherence at the group level was significantly associated with lower scores on measures of verbal encoding and RM (Obermeit et al., 2015). Furthermore, participants with mixed encoding and retrieval profiles were

significantly more likely to evidence adherence failures than participants with intact memory or encoding deficits.

*Prospective Memory*

Despite the relative nascence of the literature, PM appears to be an important component of cART adherence (for a review, see Zogg et al., 2012). Woods and colleagues conducted a series of studies to evaluate whether PM accounted for cART adherence failures independently from established predictors of non-adherence. In one study, higher frequency of PM complaints and performance deficits on PM tasks were independently related to poorer self-reported medication management (Woods et al., 2008b). Hierarchical regression analyses revealed that self-reported and objective PM measures together explained unique variance in medication management over and above established predictors of nonadherence, including mood disorders, environmental structure, psychosocial variables, and deficits in RM and executive functions. This study was the first to support incremental ecological validity of PM for predicting cART adherence. In a follow-up study, non-adherent participants demonstrated significantly worse time-based PM than adherent participants (Cohens *d*= -.54; Woods et al., 2009a). Loss-of-time errors on the laboratory PM task conferred a near-sixfold increase in the likelihood of being in the non-adherent group. Logistical regression analyses revealed that strategic aspects of PM (i.e., time-based PM) uniquely and independently predicted cART nonadherence, even after consideration of other established predictors of nonadherence, including RM and psychiatric comorbidities (Poquette et al., 2013; Woods et al., 2009a).

*Compensatory Strategies*

As both RM and PM deficits predict cART nonadherence, strategies that support appropriate detection and recall of cART dosing information are particularly relevant for persons with HIV-associated memory impairments. Specifically, these *compensatory strategies* are discrete behaviors that can circumvent reliance on depleted cognitive resources usually necessary for memory-related adherence tasks (e.g., self-directed storage and retrieval (RM); and/or strategic processes of intention encoding and retrieval (PM)).

In the case of impaired RM, reliance on self-directed storage and retrieval often results in failure to access necessary information. For example, more complex medication regimens are known to disproportionately impact cART adherence for persons with HIV-associated memory impairments (Hinkin et al., 2002). Similarly, repeating prescription instructions to oneself to facilitate later recall is not associated with better adherence when RM deficits are present (e.g., Blackstone et al., 2013). Conversely, strategies that compensate for these resources have been shown to improve performance on adherence-related RM tasks. Simplification of cART regimens is known to benefit adherence (e.g., Nachega et al., 2014), perhaps because of decreasing demands on retrieval by reducing the amount of information to be retrieved; and in response, many cART regimens have become available as once-daily tablets.

For impaired PM, reliance on strategic processes of intention encoding and retrieval can result in failures at any or all PM stages. Thus, strategies purported to support PM processing in the context of strategic deficits are thought to do so by shifting the nature of required resources away from strategic processes toward more automatic processes. For example, several strategies are thought to strengthen the cue-intention pairing, which in turn reduce reliance on strategic processes during the delay interval and/or increase activation of the cue-intention pairing; both mechanisms would support cue detection and ultimately improve PM (Faytell et al., in press). Such strategies include errorless learning (e.g., Clare & Jones, 2008), spaced retrieval (Camp, Foss, Stevens, & O'Hanlon, 1996), visualization (e.g., Faytell et al., in press), and implementation intentions (e.g., Burkard et al., 2014). As adherence is a naturalistic activity that conceptually maps onto PM (Park & Kidder, 1996; Zogg et al., 2012), many of these strategies have potential for supporting adherence-related PM tasks, though formal scientific evaluations are always prudent.

Still other strategies support RM and PM simultaneously. For example, use of an electronic device that provided verbal reminders at dosing times was associated with significantly better adherence for participants with HIV-associated memory impairments (Andrade et al., 2005). This strategy supports RM by externalizing the storage and retrieval of dosing information. Such externalization of crucial information is thought to decrease reliance on self-directed resources, which in turn decreases the

likelihood of access failures and ultimately results in better adherence. The same strategy also supports PM, as the verbal reminders at dosing times represent highly salient cues. Highly salient cues are distinctive and noticeable; such characteristics attract attention more automatically, and facilitate the shift from ongoing task to the intended action, thus supporting cue detection and ultimately improving adherence (e.g., Mahy, Moses, & Kliegel, 2014). Thus for ease of language, the discussion will shift to general memory-related compensatory strategies.

Many strategies promoted by the intervention literature have demonstrated generally positive benefits for adherence among persons with HIV-associated memory impairments. Such evidence-based strategies include one-way (Safren et al., 2003) and two-way (e.g., Hardy et al., 2011) text-messaging or beeper systems, self-monitoring (e.g., with a daily pill diary; Safren et al., 2001), and brief psychoeducational interventions promoting RM and PM approaches for supporting adherence (Safren et al., 2001).

However, very few studies have identified strategies that are self-implemented and used successfully in daily life. The most common strategy is reliance on pill box organizers, with employment endorsed by 39-72 percent of participant samples (e.g., Catz et al., 2000; Kalichman et al., 2005). Self-initiated pill box use occurs more frequently among women and HIV+ individuals with history of high adherence, and less frequently among HIV+ individuals who are ART naïve, homeless, or have a more complicated cART regimen (Petersen et al., 2007). Other commonly implemented strategies include beepers or timers (27%), reminder notes (27%), and datebooks (15%; Kalichman et al., 2001); use of mealtimes (82%), bedtime (74%), or other daily activities (72%) as cues for taking medications (Catz et al., 2000); and a variety of internal memory-reliant strategies (Blackstone et al., 2013).

Pill box implementation is also the most successful strategy; in one study, pill box users were significantly more likely to evidence undetectable viral loads, and were less likely to have missed a medication dosage within a day of the study assessment (Kalichman et al., 2005). In another study, pill box use was associated with 4.1-4.5 percent improvements in cART adherence, 0.34-0.37 $\log_{10}$ copies/ml

decreases in viral load, and 14.2-15.7 percent greater likelihood of evidencing viral loads below 400 copies/ml (OR=1.8-19; Petersen et al., 2007).

**Frequency of Strategy Use**: More frequent use of compensatory strategies is associated with many clinicodemographic and neurocognitive factors, including older age (e.g., Weber et al., 2011), non-Caucasian racial/ethnic group, greater number of cART or non-cART prescriptions, diagnosis of AIDS, current affective distress, lifetime history of major depressive disorder, worse global neuropsychological performance, worse event-based PM, unemployment, and dependence for instrumental activities of daily living (Blackstone et al., 2013).

Data are mixed regarding the implications of frequent vs. infrequent strategy use for adherence. Some studies have reported significant associations between frequent strategy use and better performance on PM tasks (e.g., Aronov et al., 2015), while other studies have reported the opposite finding (e.g., Blackstone et al., 2013). For example, one study found an association between higher frequency of strategy use and worse cART adherence among HIV+ adults (Blackstone et al., 2013). Conversely, another study reported that success on a naturalistic PM task was indirectly associated with greater daily use of PM-based and external compensatory strategies among older but not younger HIV+ adults (Weber et al., 2011). Clearly, further investigation is necessarily for elucidating the relationship between the frequency of compensatory strategy use and level of adherence.

## Fatigue

### *Prevalence and Definitions*

Fatigue is a universal symptom associated with most illness, both acute and chronic (Aaronson et al., 1999). It is also associated with normal daily functioning among healthy populations. Fatigue is one of the most common complaints of patients in primary health care settings (Aaronson et al., 1999). Despite its universal prevalence - or perhaps because of it - fatigue continues to be a poorly understood construct. Current lack of understanding is due in part to the nature of fatigue. Fatigue is a highly complex symptom that can involve interactions between biological processes, psychosocial phenomena, and behavioral manifestations (Aaronson et al., 1999). Unsurprisingly, a universal definition of fatigue is

difficult to generate. Historically, characterizations of fatigue have relied on dichotomizing fatigue into (1) peripheral versus central; and (2) acute versus chronic. Peripheral fatigue is defined as functional organ or muscle failure, which is attributable to excessive energy consumption (e.g., Berger et al., 1991), and/or peripheral nervous system disorders (e.g., Chaudhuri & Behan, 2004). Peripheral fatigue is quantifiable through measurement of corresponding depletions of hormones, neurotransmitters, or other substrates of physiological functions (Berger et al., 1991). Conversely, central fatigue is subjective sense of fatigue perceived at the level of the central nervous system (Chaudhuri & Behan, 2004). Central fatigue is characterized by reduced endurance of sustained mental and/or physical activities, accompanied by greater perceived effort (Chaudhuri & Behan, 2004). Central fatigue is associated with a broad range of autonomic, peripheral, and central nervous systems disorders (Jason, Evans, Brown, & Porter, 2010).

Fatigue is also dichotomized by chronicity (e.g., Piper, 1989). Acute fatigue is characterized by rapid onset, short duration, and amelioration through diet, exercise, rest, and management of stress (for a review, see Piper, 1989). Acute fatigue is reported by about seven to 45 percent of the general population (Lewis & Wessely, 1992). It is thought to serve a protective function; have a unitary cause; occur primarily in healthy individuals; and be perceived as normal. Expected effects of acute fatigue on activities of daily living are subtle or minor. In contrast, chronic fatigue has an insidious onset, pervasive duration, and is not ameliorated through similar restorative techniques (Piper, 1989). Chronic fatigue is also characterized as serving an unknown purpose or function; associated with additive, multiple, or unknown causes; and perceived as unusual, abnormal, or excessive. Chronic fatigue is expected to have significant effects on quality of life and performance of activities of daily living. Chronic fatigue is most prevalent and debilitating in the context of chronic medical illnesses, such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and of course, HIV (see Swain, 2000 for a review). Chronic fatigue is also common in the general population; prevalence of fatigue lasting more than six months is about 10 to 20 percent among primary care patients, and drops to about one to three percent in community samples (e.g., Swain, 2000).

Aaronson and colleagues (1999) argued that these dual approaches fail to capture the true complexities of the fatigue experience. Specifically, Aaronson et al. (1999) expressed concern that these definitions of fatigue failed to incorporate a biobehavioral framework that reflected contributions from physiological and psychological functioning or social and cultural factors relevant to the experience of fatigue. Driven by these concerns, they produced an alternate conceptualization of fatigue, as "the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity (Aaronson et al., 1999)." As described by Aaronson et al. (1999), awareness of fatigue is required due to the inherently subjective nature of the phenomenon. Resources describe a range of factors that can include biochemical properties, psychological functioning, and the social and cultural factors that modify how individuals interpret or respond to the experience of fatigue. Utilization and restoration are processes through which resources are deployed and replenished to support activity. Thus, fatigue is conceptualized as the result of imbalance in this system (e.g., when sufficient resources are unavailable because demand is too great, or because the processes of utilization and restoration are disrupted, etc.).

### *Fatigue and HIV*

#### *Prevalence and Profile*

Among persons living with HIV disease, fatigue is the most commonly reported constitutional symptom (e.g., Perdices et al., 1992), with estimated prevalence ranging between 33 and 88 percent (Jong et al., 2010). Often, fatigue is reported as the most distressing physical symptom (e.g., Duran et al., 2001) and does not remit spontaneously (Barroso et al., 2015). Fatigue is associated with affective distress, particularly depression (e.g., Ferrando et al., 1998), but has also demonstrated independent contributions to disability and physical limitations (e.g., Ferrando et al., 1998). Fatigue is more prevalent among HIV+ individuals who take cART (Jong et al., 2010), and among HIV+ individuals with lower or inadequate income, unemployment, more childhood trauma, and presence of recent stressful events (Jong et al., 2010; Leserman et al., 2008).

*Etiology*

The etiology of fatigue in HIV disease is dynamic and multifaceted, with contributions from the inflammatory actions of HIV infection, interactions with other HIV-related symptoms, and side-effects of antiretroviral medications.

**Disease and Immunologic Correlates***:* Investigations of associations between fatigue and physiologic markers of HIV disease and immunologic response have produced mixed results. In one study, HIV+ individuals who reported that fatigue interferes with daily functioning evidenced significantly lower CD4 levels, higher total globulin, and lower hemocrit levels than HIV+ individuals who did not report fatigue (Darko et al., 1992). Another study reported significant associations between fatigue severity and thyroid-stimulating hormone, platelets, and alkaline phosphatase (Barroso, Carlson, & Meynell, 2003). A third study found a higher prevalence of fatigue among seropositive participants with CD4 counts less than 500 compared to seronegative participants or HIV+ participants with CD4 counts over 500 (Ferrando et al., 1998). In another study, fatigue severity was associated with levels of low-abundance plasma proteins, including apolipoprotein B, histidine-rich glycoprotein, alpha-1 B glycoprotein, and orosomucoid 2 (Jensen et al., 2014). Conversely, other studies found no relationship between fatigue and physiological biomarkers, including CD4 (Barroso, Carlson, & Meynell, 2003); HIV RNA viral load (Ferrando et al., 1998); hematocrit levels, hemoglobin levels, red blood cell counts, or serum erythropoietin (Jong et al., 2010).

**Interactions with Sleep and other HIV-Related Symptoms**: Unsurprisingly, HIV-related fatigue is strongly and inextricably linked with sleep. Sleep quality (e.g., Phillips et al., 2004; Salahuddin et al., 2009), sleep duration, and witnessed episodes of sleep disturbance (e.g., sleep apnea; Goswami et al., 2015) are all strong independent predictors of fatigue. Intensity of fatigue has been linked to poor nighttime sleep and daytime sleepiness (Salahuddin et al., 2009). Like fatigue, sleep disturbance is a common complaint in HIV disease, with prevalence estimates between 10 and 100 percent (see Wu et al., 2015 for a meta-analysis). Alterations in sleep are known to occur early in the course of infection (e.g., Norman, Chediak, Kiel, & Cohn, 1990), and continue to worsen across the disease course (e.g., Darko et

al., 1992). Recent data support an association between sleep disturbance and inflammation (Gay et al., 2015), suggesting that poor sleep quality may be partly related to the inflammatory effects of HIV infection.

Other HIV-related symptoms have moderating and mediating interactions with fatigue and with one another (Lenz et al., 1997). For example, pain symptoms can cause both sleep dysfunction and fatigue, which in turn can worsen the experience of pain (e.g., Wilson et al., 2016). Among seropositive populations, fatigue is most strongly predicted by comorbid neuropsychiatric symptoms (Jong et al., 2010), particularly depression (e.g., Ferrando et al., 1998). Severity of depressive symptoms predicts greater fatigue intensity (Leserman et al., 2008; Perkins et al. 1995) and fatigue-related impairments in daily functioning (Leserman et al., 2008), while fatigue and/or sleep disturbance at the time of antidepressant initiation or adjustment has predicted slower time to first remission of a depressive episode (Sowa, Bengtson, Gaynes, & Pence, 2016). In one study, 67 percent of the variance in intensity of fatigue was attributed to sleep quality state anxiety, depression, and other HIV-related symptoms (Phillips et al., 2004). Anxiety (Barroso, Carlson, & Meynell, 2003; Sewell et al., 2000) and perceived stress (Hand, Phillips, & Dudgeon, 2006) are also significantly associated with fatigue severity.

**Relationships with cART and Sleep:** Although HIV-related fatigue and sleep disturbance occur in the absence of pharmacologic therapy (e.g., White, Mitler, & Darko, 1995), these symptoms are also common side effects of antiretroviral medications. For example, initiation of efavirenz, a non-nucleoside reverse transcriptase inhibitor, is commonly associated with sleep disturbances, including insomnia, hypersomnia, reduced diurnal concentration, and vivid dreams (e.g., Moyle et al., 2006). In one study, initiation of efavirenz-based monotherapy was associated with modest but objective changes in sleep architecture that appeared to partially resolve by 12 weeks, though patient self-report indicated that perceived treatment-emergent effects on sleep and diurnal function persisted to the 12-week follow-up (Moyle et al., 2006).

Unsurprisingly, fatigue and sleep disturbances are also commonly reported side effects of cART regimens. For example, in a trial comparing a regimen of abacavir, lamivudine, and efavirenz regimen to a zidovudine (a nucleoside analog reverse-transcriptase inhibitor), lamivudine, and efavirenz regimen,

sleep disorders, abnormal dreams, and fatigue were all commonly (> 1 % incidence) reported drug-related adverse events, with sleep disorders reported by six to seven percent of patients, abnormal dreams reported by four to five percent of patients, and fatigue reported by six to eight percent of patients (DeJesus et al., 2004). In a more recent trial comparing a regimen comprised of lamivudine, abacavir (another nucleoside analogue reverse transcriptase inhibitor), and dolutegravir (an integrase strand transfer inhibitor; INSTI) to a regimen comprised of efavirenz, tenofovir disoproxil fumarate (a nucleoside analogue reverse transcriptase inhibitor), and emtricitabine (a nucleoside reverse transcriptase inhibitor), insomnia was reported by four percent of patients in each trial arm (Walmsley et al., 2013).

*Relationship with Neuropsychological Functioning*

Few studies have evaluated the relationship between cognitive factors and fatigue in the context of HIV. Of those studies, most of them have limited their investigations to examining the direct relationship between fatigue and neuropsychological functioning (e.g., Millikin et al., 2003; Perkins et al., 1995). Findings elucidating the nature of the relationship between fatigue and neuropsychological functioning have produced largely null results, as most studies have reported no significant link between fatigue and neuropsychological performance (e.g., Heaton et al., 1995; Millikin et al., 2003). Other investigations have revealed only modest and limited associations between fatigue and neuropsychological functioning within specific cognitive domains. For example, Perkins and colleagues (1995) reported that while fatigue was not directly related to overall neuropsychological functioning, increases in fatigue over six months were associated with decrements in motor functioning. Similarly, while Heaton et al. (1995) did not find an association between fatigue severity and neuropsychological performance in a large cohort of pre-cART HIV+ individuals, they reported a small trend-level relationship between fatigue and neuropsychological performance when fatigue was treated as a dichotomous variable (present vs. absent). This pattern of findings regarding the relationship between fatigue and neuropsychological functioning are consistent with data from other clinical populations (e.g., multiple sclerosis and traumatic brain injury) as well as healthy adults (see Strober & DeLuca, 2013 for review).

*Functional Impact*

Fatigue is strongly correlated with numerous measures of daily functioning (e.g., Henderson et al., 2005) and overall quality of life (e.g., Breitbart et al., 1998) in HIV disease. It is associated with ratings of physical health (e.g., Voss, 2005), mental health (e.g., Cunningham et al., 1998), and health-related quality of life (e.g., Cleary et al., 1993). Fatigue has been shown to predict limitations in activities of daily living (Cleary et al. 1993; Ferrando et al., 1998), such as interference with employment and driving (Darko et al., 1992), and is strongly correlated with level of physical functioning (Breitbart et al., 1998) in HIV disease.

***Fatigue and cART Adherence***

Patients sometimes report feeling "too tired" to take medication when asked why they failed to adhere (e.g., Siegel, Schrimshaw, & Raveis, 2000). Fatigue is often included in symptom constellations that predict adherence (e.g., Holzemer et al., 1999; Molassiotis et al., 2002), and appears to influence the relationship between sleep quality and cART adherence. Moderate to severe levels of poor sleep quality are independently associated with cART adherence (e.g., Tello-Velasquez et al., 2015); in one study, self-reported insomnia conferred more than twofold greater risk of nonadherence to cART (OR: 2.32; Ammassari et al., 2001). However, Dalmida, Holstad, Fox, & Delaney (2015) observed a significant mediating effect of fatigue on the relationship between sleep quality and cART adherence. Specifically, as fatigue increased, the relationship between sleep quality and adherence weakened, and fatigue became a stronger predictor of adherence. Despite ample data supporting such indirect effects of fatigue on adherence, there is a paucity of studies that investigate independent effects of fatigue on cART adherence. Results of these few studies suggest that fatigue is a strong predictor of adherence. In one study, self-report of fatigue conferred more than twofold greater risk of cART nonadherence (OR=2.1. 95% CI=1.2-3.7; Trotta et al., 2003). In another study, identification of fatigue as an adverse side effect of cART was strongly associated with worse adherence (OR=1.4, 95% CI=1.2-1.6; Johnson et al., 2005).

### *Summary*

Overall, investigations of fatigue among HIV+ populations have focused on four major areas of study: (1) the prevalence, severity, and course of fatigue in HIV; (2) physiological, psychological, and/or psychosocial predictors and covariates of fatigue in HIV; (3) the effects of fatigue on daily functioning and health-related outcomes; and (4) the relationships between fatigue and neuropsychological performance. Findings from the first three areas of study present a troubling picture of fatigue in HIV. Fatigue is common, chronic, and distressing; it occurs more frequently in vulnerable populations (e.g., among populations with lower socioeconomic status and/or comorbid neuropsychiatric symptoms); and it predicts worse daily functioning outcomes, including suboptimal adherence.

## The Impact of Fatigue and Memory Impairment on cART Adherence

In summary, the following discrete elements of the interrelationships between fatigue, HIV-associated memory impairment, and cART adherence are known: (1) fatigue and memory impairment each demonstrate effects on adherence when studied in isolation; (2) the effect of fatigue on adherence is independent of sleep quality; (3) retrospective memory and prospective memory exert independent effects on adherence; (4) compensatory strategy use is associated with adherence, though the nature of the relationship remains elusive; and (5) fatigue does not generally predict decrements of retrospective or prospective memory performance. Otherwise, the interrelationships between fatigue, memory impairment, and cART adherence are not well understood. For example, no studies to date have tested for an association between fatigue and frequency of compensatory strategy use among persons with HIV-associated memory impairments. However, a strong association between fatigue and greater endorsement of memory strategies has been observed in a large sample of community-dwelling adults with multiple sclerosis (OR: 1.27, $p < 0.001$; Johnson et al., 2009), suggesting there may be a similar link present among seropositive populations.

### *Our Working Models*

Conceptually, we drew from Aaronson and colleagues' (1999) model of fatigue, as well as the multiprocess model of PM introduced by Einstein & McDaniel (2005), and later adapted by Kliegel and

colleagues (2008), to produce theory-driven hypotheses about the interrelationships between fatigue, memory impairment, and cART adherence. According to the Aaronson et al. (1999) fatigue model, the effect of fatigue on adherence is thought to result from decreased capacity for completing a task due to lack or imbalance of necessary resources. Extending the Aaronson et al. (1999) model to cognition, we expected that the effect of memory impairment on adherence also reflects decreased capacity for task completion due to inadequate resources (i.e., PM- and/or RM-related resources). The putative role of compensatory strategies is to circumvent reliance on said resources, thus bolstering adherence. Thus, we predicted that fatigue would dampen the efficacy of adherence-related compensatory strategies for memory impaired participants.

Ultimately, elucidation of the interrelationships between fatigue, memory impairments, and cART adherence provide valuable clinical information that could inform efforts to (1) improve patient-specific targeting of fatigue-related assessments and interventions; and (2) develop effective interventions for bolstering adherence in seropositive populations.

**Aims and Hypotheses**

***Aim 1***

Our first aim was to investigate the nature of the interrelationships between fatigue, memory impairment, and cART adherence. We generated two directional hypotheses and one exploratory hypothesis regarding this aim.

**Hypothesis 1**: We predicted that fatigue and memory impairment will have a synergistic effect on cART adherence, such that individuals with both memory impairment and fatigue would demonstrate significantly worse adherence than persons with either factor alone, or with neither factor.

**Exploratory Hypothesis 2**: We explored whether fatigue affects the relationship between memory impairment and cART adherence directly, or whether it acts indirectly on this relationship by influencing the frequency of strategies used to compensate for memory impairment, which was expected to mediate the relationship between memory impairment and adherence.

**Covariate Hypothesis**: We predicted that other clinicodemographic variables known to have strong associations with adherence would not better explain the significant relationships between fatigue, memory impairment, and adherence.

***Aim 2***

Our second aim was to investigate whether changes in fatigue, strategy use, and memory impairment over a one-year period were associated with changes in perceived medication management efficacy. We generated four directional hypotheses regarding this aim.

**Hypothesis 3**: We expected that changes in fatigue would be significantly associated with changes in perception of medication management efficacy, such that greater increases in fatigue would be associated with greater decreases in perceived efficacy.

**Hypothesis 4**: We also expected that change in the number of strategies employed would be associated with changes in perceived efficacy, such that greater increases in the number of strategies employed would be associated with greater decreases in perceived efficacy.

**Hypothesis 5**: We also expected that changes in RM and PM would be significantly associated with changes in perception of medication management efficacy, such that greater decreases in memory performance on measures of RM and PM would be associated with greater decreases in perceived efficacy.

**Hypothesis 6**: Finally, we hypothesized that the data would be best fit by a model of the associations between changes in fatigue, strategy use, and perceived efficacy.

# METHODS

## Participants

Data from this retrospective study were collected in compliance with regulations mandated by the Institutional Review Board of University of California, San Diego. Approval by the University of Houston Committee for the Protection of Human Subjects was obtained for this archival study. Permission to use the archival data was obtained from Dr. Steven Paul Woods. Data were selected from 177 adults with HIV infection who were previously enrolled in NIH Grant R01-MH73419. Inclusion criteria for the original study included diagnosis of HIV infection and demonstration of capacity to provide consent on the day(s) of study evaluation. HIV serostatus was confirmed using standard Western blot and/or a point-of-care test (MedMira Inc., Nova Scotia, Canada). Exclusion criteria included potential psychotic disorders or neurological conditions known to negatively affect cognition (e.g., seizure disorder, traumatic brain injury with loss of consciousness greater than 15 minutes), estimated verbal IQ scores < 70 (based on the Wechsler Test of Adult Reading [WTAR]; Psychological Corporation, 2001), current substance abuse or dependence within 30 days, or urine toxicology screen positive for illicit substances on the day of baseline testing. Inclusion criteria for Aim 1 of the present study included completion of the Fatigue-Inertia subscale from the Profile of Mood States and at least one measure of cART adherence. Inclusion criteria for Aim 2 included completion of both the Fatigue-Inertia subscale from the Profile of Mood States and the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence questionnaire (BERMA MMES) at both time points.

## Materials and Procedure

After providing written informed consent, all participants were administered a semi-structured clinical interview to collect relevant clinicodemographic information. Participants represented a diverse clinical sample (see Table 1). HIV infection and treatment variables were obtained through a physical evaluation by research nurses, a blood draw, and available clinic medical records (Table 2). Pill burden was measured by recording the number of current ARV and non-ARV medications reported by each participant. High cART and non-cART pill burdens were assigned to participants who reported more than

the median numbers of medications. Overall pill burden was also calculated from the total number of current cART and non-cART medications.

Participants were administered a research neuropsychological assessment battery to assess the key cognitive domains highlighted by the Frascati criteria for HAND diagnosis (Antinori et al., 2007), including learning, memory, attention, executive functions, processing speed, and motor skills. Classification of HAND was determined by converting raw scores on these measures into *T*-scores correcting for age, gender, education, and ethnicity when appropriate. These *T*-scores were then transformed into a global rating score, which ranged from 0 (*above average, T*-score ≥ 55) to 9 (*severely impaired, T*-score < 20), with global ratings greater than 4 indicating a positive diagnosis of HAND (Woods et al., 2004). Participants were also administered a series of questionnaires to assess current and lifetime psychiatric diagnoses (Table 1), adherence, fatigue, and compensatory strategy use (Table 3).

All measures were administered by trained research assistants and scored in accordance with published manuals. cART adherence was also obtained behaviorally through utilization of MEMS caps, as described below. Re-administration of these materials (except the MEMS caps assessment) was conducted with a subset of participants, who returned for follow-up evaluations approximately one year later (N=57; mean test-retest interval=422 +/- 65 days).

***Medication Adherence Assessment***

General medication management abilities were assessed using the 20-item Medication Management Efficiency Scale (*MMES*) from the Beliefs Related to cART Adherence (BERMA MMES; McDonald-Miszczak et al., 2004) questionnaire. Each BERMA MMES item was rated on a 5-point Likert scale, which range from 1 (*strongly disagree*) to 5 (*strongly agree*); total scores range from 20 -100. Reverse scoring is applied to several items so that higher scores on the BERMA MMES scale reflect better perceived medication management efficacy. The BERMA has excellent overall reliability (Cronbach's alpha =.94; McDonald-Miszczak et al., 2004), split-half reliability (Spearman-Brown =.91; Woods et al., 2008b), and internal consistency (Cronbach's alpha =.93; Woods et al., 2008b).

Self-reported adherence was assessed with an item from the NIAID AIDS Clinical Trials Group (ACTG) Adherence to Anti-HIV Medications (4 days) (Chesney et al., 2000), which assesses cART adherence over the last four days (e.g., "How many pills did you skip taking yesterday/2 days ago/3 days ago/4 days ago?") Participant adherence rates were calculated for each of the four days as 1 – (number of pills missed for the day/number of pills prescribed); these daily rates were averaged and multiplied by 100 to produce the ACTG summary adherence rate.

Medication event monitoring system (MEMS) caps were used to measure cART adherence over a three-to eight-week period (Mean= 39.8 days, SD=9.4). MEMS caps are medication bottle caps fitted with a pressure-activated microprocessor. Each time the bottle is opened, the microprocessor automatically records the date, time, and duration the bottle remains open. Participants received the MEMS caps at the time of study assessment. They were instructed to use the MEMS capped bottles to dispense only their cART medication, and to take their medication as prescribed by their physician. They were cautioned not to open the bottles unless they were about to take a dose, and not to "pocket dose" (e.g., removing more than one dose at a time). MEMS caps were collected and the data were downloaded when participants returned for the follow-up appointment five weeks later. Rates of adherence were calculated by dividing actual dosing events by the number of prescribed doses, then multiplying by 100. When MEMS caps events exceeded the number of prescribed doses, the excess number of events was subtracted from the total.

MEMS assessments sometimes underestimate adherence, while self-report measures can overestimate adherence (e.g., Arnsten et al., 2001); thus, multiple objective and self-report methods of adherence measurement are often preferable to a single method approach (Liu et al., 2001). MEMS adherence rates tend to be at least moderately correlated with self-report questionnaires (Shi et al., 2010). Thus, we incorporated the raw data from the three measures (i.e., the BERMA MMES total scores, ACTG adherence rates, and MEMS adherence rates) into a cART adherence latent variable. For descriptive purposes, ACTG and MEMS adherence rates were also dichotomized as either "Adherent" or "Non-

Adherent" based on the 90 percent threshold consistent with historical definitions of adherence (e.g., Woods et al., 2009a). Dichotomized ACTG and MEMS scores are presented in Table 3.

***Retrospective Memory Assessment***

Retrospective memory (RM) was assessed with the Delayed Free Recall scores from the California Verbal Learning Test – Second edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) and Logical Memory subtest from the Wechsler Memory Scale III (LM II; Psychological Corporation, 1997). The CVLT-II is comprised of a list of 16 nouns read aloud at a rate of slightly longer than one word per second, after which participants are instructed to recall aloud as many words as they can. After five learning trials, a second list of 16 distractor nouns is read aloud and participants are again instructed to repeat as many as possible. Participants are then instructed to recall aloud words from the first list. After a 20-minute delay, participants are again instructed to recall as many words from the first list as they can. The CVLT-II delayed free recall was determined as the total number of words freely recalled following the 20-minute delay, converted into a sample-based z-score. LM assesses recall and recognition of two brief stories. After each story was read aloud, participants were instructed to recall aloud as much detail as they could remember. Thirty minutes later, participants were again asked to recall aloud as many details from each story as they could remember. The LM delayed free recall score was comprised of the total number of correctly recalled story details following the 30-minute delay, converted into a sample-based z-score. The delayed free recall z-scores from the CLVT-II and LM were averaged to create a RM composite score for each participant. Because CVLT-II and LM scores were highly correlated ($r_s$= .526, $p$<.0001), the LM z-score was used in place of the retrospective memory composite score for the single participant with missing CVLT-II data.

***Prospective Memory Assessment***

To assess prospective memory (PM), all participants completed the research version of the Memory for Intentions Screening Test (MIST; Raskin, 2004; Raskin, Buckheit, & Sherrod, 2010; Woods et al., 2008c). The MIST is a standardized performance-based measure developed to assess multiple elements of prospective memory. Participants perform four time-based and four event-based prospective

memory tasks during a 30-minute period. Simultaneously, they are engaged in a word-search puzzle as the ongoing distractor task. Test tasks are balanced across delay intervals (i.e., two-minute or 15-minute delay) and response modalities (i.e., verbal or physical). Thus, as well as providing a summary score, the MIST permits calculation of subscales based on cue type, delay interval, and response modality. Total score for each subscale falls between zero and eight. The MIST also provides a brief 24-hour interval task in which participants are instructed to call the examiner and leave a message specifying the number of hours slept the night after the study evaluation. Total score for this subscale ranges between zero and two. The MIST has adequate inter-rater reliability and split-half reliability (Woods et al., 2008c), and acceptable construct validity among samples of healthy adults (Carey et al., 2006; Raskin, 2004), individuals with schizophrenia (Woods et al., 2007b), and persons with HIV disease (Carey et al., 2006; Woods et al., 2006). The 15-minute interval MIST subscale was selected for analysis due to its sensitivity for predicting non-adherence independent of demographic, mood, and cognitive functioning variables, as well as self-reported adherence (Poquette et al., 2013). The 24-hour subscale was also selected to provide an additional measure of longer PM delay. Sample-based z-scores of the MIST 15-minute and 24-hour subscales were generated and averaged together to create the PM composite score.

***Fatigue Measure (POMS)***

Self-reported fatigue was collected using the Fatigue-Inertia subscale of the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981). The POMS is a 65-item self-report measure for which participants are instructed to rate adjectives (e.g., *listless*) and brief phrases (e.g., *worn out*) using a 5-point Likert-type scale that ranges from 0 (*not at all*) to 4 (*extremely*). Thus, higher scores indicate greater distress. The POMS was originally developed to measure changes in mood following psychotherapy (McNair, Lorr, & Droppleman, 1981), The POMS has also been used to assess mood in a variety of medical populations, including patients with spinal cord injury (e.g., Rodrigues et al., 2013); cancer (e.g., Yellen et al., 1997), sleep disorders (e.g., Lee, Hicks, & Nino-Murcia, 1990), and most importantly, HIV (e.g., Patterson et al., 2006), as well as psychiatric (e.g., Norcross, Guadagnoli, & Prochaska, 1984), and healthy (e.g., Barker-Collo, 2003; Nyenhuis et al., 1999) populations. The POMS

is an internally consistent, multidimensional measure with a stable factor structure (Norcross, Guadagnoli, & Prochaska, 1984), adequate internal consistency, and good convergent item validity (Reddon, Marceau, & Holden, 1985).

The POMS Fatigue-Inertia subscale (POMS-FI) is represented by a stable unidimensional factor structure (Norcross, Guadagnoli, & Prochaska, 1984), and demonstrates sufficient psychometric properties, including adequate internal consistency, test-retest reliability, construct validity, and convergent validity across multiple investigations (e.g., Impellizzeri et al., 2013; Lee, Hicks, & Nino-Murcia, 1990; Yellen et al., 1997). The POMS-FI has been selected by multiple investigations to assess fatigue among HIV+ populations (Cole, Kemeny, & Taylor, 1997; Gifford et al., 1998; Montoya et al., 2013; Osowiecki et al., 2000; Weber et al., 2013). The POMS-FI is comprised of the following seven items: *worn out, listless, fatigued, exhausted, sluggish, weary,* and *bushed*. The POMS-FI total score was calculated by summing the individual item ratings, and ranges from 0 (*no symptoms of fatigue*) to 28 (*severe symptoms of fatigue*).

***Compensatory Strategy Use***

Participants were administered the Prospective Memory for Medications Questionnaire (PMMQ; Gould, McDonald-Miszczak, & King, 1997; Gould, McDonald-Miszczak, & Gregory, 1999), a 28-item measure that assesses how frequently participants use a variety of cognitive (e.g., *do you regularly repeat to yourself the instructions for taking a prescription…?*) and behavioral (e.g., *do you use a clock or watch alarm to remind you when it is time to take your medications?*) medication-taking strategies. Participants rated how often they utilize each strategy using a 5-point Likert-type scale similar to the POMS. Item responses range from 0 (*never*) to 4 (*always*), with higher overall scores indicating more frequent strategy use. Compensatory strategy use (CSU) frequency scores (Aim 1) were calculated by summing participant ratings across all items, and range from 0 to 112. CSU number scores (Aim 2) were calculated by adding the number of strategies participants endorsed using and dividing that sum by the total number of queried strategies (28), then multiplying by 100 for a percentage score that ranged from 0 to 100. Thus, higher

CSU number indicates employment of a greater number of different strategy types, but does not reflect the frequency to which these strategies are employed.

***Neuropsychiatric Assessment***

Participants were also administered the Composite International Diagnostic Interview (CIDI version 2.1; World Health Organization, 1998), which was used to provide current and lifetime diagnoses of Major Depressive Disorder, Generalized Anxiety Disorder, and Substance Use Disorders per *Diagnostic and Statistical Manual of Mental Disorders* ($4^{th}$ Ed.; American Psychiatric Association, 1994) criteria. To assess the influence of depressive symptomatology on the model(s), the Depression-Dejection subscale of the POMS (i.e., POMS-DD) was also used. This subscale is comprised of 15 items rated on the same Likert scale as the POMS-FI, with a total score that ranges from 0 to 60. This subscale has high internal consistency among healthy and medical populations (rs=.94- .96; Curran, Andrykowski, & Sudts, 1995) and has been used in prior studies to assess depressive symptomatology among HIV-positive populations (e.g., Castellon et al., 2006) and in concert with clinician rating scales of depression, such as the Hamilton Rating Scale (HAM-D; Perkins et al., 1995). The POMS-DD has shown high predictive validity for differentiating current major depressive disorder (MDD; determined by SCID interview) from somatic symptoms of HIV, and has performed comparably with the Cognitive-Affective scale from the Beck Depression Inventory (Patterson et al., 2006), another measure validated for sensitive detection of MDD in HIV-positive populations (e.g., Kalichman, Rompa, & Cage, 2000).

**Data Analyses**

The dataset was evaluated for outliers and missing data points. All continuous variables were screened for normality, and findings associated with non-normally distributed variables were reassessed with a non-parametric approach. All skewness and kurtosis values were below problematic levels (Kline, 2011). For all analyses, the critical alpha was set at .05. JMP (Jones & Sall, 2011) and Microsoft Excel (2013) were used for data cleaning, computing descriptive statistics, and conducting correlational analyses, while AMOS (Arbuckle, 2016) was used to build and evaluate path models using structural equation modeling (SEM).

***Structural Equation Modeling (SEM)***

*Path Analysis/SEM*

Path analysis is an extension of multiple regression. Specifically, it is a series of multiple regression equations that together establish a pattern of relationships among a group of variables and evaluate the degree to which the data fit these hypothesized relationships (Klem, 1995). Path analysis provides hypothesized causal models that clearly state the predicted relationships among a group of variables, and provide magnitude estimates of the hypothesized relationships (Klem, 1995). This approach was selected because it permits comparisons of different hypothesized models of the relationships between fatigue, memory impairment, and cART adherence. Path analysis was conducted with a structural equation modelling approach to permit incorporation of more complex modeling structures (e.g., modelling MEMS, BERMA MMES, and ACTG scores as indicators of a latent adherence variable).

*Latent Growth Modeling*

Latent growth modeling allows researchers to study the rate of change of a variable over time using multilevel models of potential growth patterns (Field 2011). Latent growth models are typically comprised of three components: the intercept, the linear component (slope), and the curvilinear component. These components are expressed with the following equation for each participant (Francis, Schatschneider & Carlson 2000):

$$Y_t = \pi_0 + \pi_1 a_t + \pi_2 a^2{}_t + \pi_3 a^3{}_t + \pi_4 a^4{}_t + \ldots + \pi_{k-1} a^{k-1}{}_t + E$$

where *k* is the number of time points, and π represents the individual's growth parameters. Parameter values are participant-specific. The growth parameters are demarcated by the numerical subscripts 0 to k - 1, and represent the order of the polynomial term. The term $a_t$ is a marker of time. The subscript t represents a given point in time from 1 to k. The term E represents random error in Y at time t, and is assumed that E is normally distributed and uncorrelated across subjects.

The intercept, expressed with the subscript 0 as $\pi_0$, is a constant and models outcome at the time point at which it is centered. The slope models a constant rate of change, and is expressed with the

subscript 1 as$\pi_1 a_t$. Finally, the curvilinear component represents changes in the rate of change (i.e., acceleration or deceleration), and at the largest can be represented by $\pi_{k-1} a^{k-1}{}_t$, or a polynomial of order k – 1 with k time points. As our data included only two time points, our latent growth models are limited to the intercept and slope and can be expressed with the simplified equation $Y_t = \pi_0 + \pi_1 a_t$.

Latent growth models are hierarchical in nature, due to the nesting of multiple time points within individual participants. Consequently, hierarchical linear modeling has been proposed as an appropriate methodology for estimating the parameters of individual growth curves (π) and analyzing the variability in these estimates (Francis, Schatschneider & Carlson 2000). However, navigating the balance between the lack of independence among the observations at the lower levels of the hierarchy and the low power for testing hypotheses on independent observations at the top of the hierarchy can be tricky. This balance has been addressed by using maximum-likelihood estimates to permit the development of multilevel models and estimation of individual parameters across all levels of the model. This approach is comprised of two simultaneous stages. The first stage is a within-participant multiple regression analysis conducted to estimate the individuals' intercept and slope parameters. The second stage is an examination of the ability of individual differences between participants to predict differences in the growth parameters, conducted as a between-participant analysis with the estimates of the intercept and slope parameters as the dependent measures.

*Model Specification*

**Exogenous and endogenous variables:** Fatigue, prospective memory (PM), retrospective memory (RM), and the product constants were generally included in path models as exogenous variables. Product constants were calculated by centering the variables at their means and then multiplying the centered variables together (e.g., for fatigue and compensatory strategy use, the product constant for participant *1* equals (POMS-FI$_1$ - POMS-FI$_{AVG}$)*(PMMQ$_1$ - PMMQ$_{AVG}$)). The adherence latent variable was always included as an endogenous variable, which indicates that it is expected to be determined by variables within the model. Compensatory strategy use (CSU) was included as either an exogenous or endogenous variable depending on the model.

**Structure:** Hypothesized non-causal associations between exogenous variables are represented by two-headed arrows, while causal associations are denoted with unidirectional arrows that extend from the exogenous variable to each endogenous variable thought to be influenced by it. Residual (or error) variables are indicated by unidirectional arrows that extend from the residual variable to the endogenous variable.

*Imputation*

Following data cleaning, the multivariate normal imputation utility available in JMP was used to fill missing continuous data points based on the multivariate normal distribution (SAS Institute, 2016). The algorithm employs least squares imputation and constructs a covariance matrix using pairwise covariances. Diagonal entries, or variances, are computed with all non-missing values for each variable, while the off-diagonal entries for any two variables are computed with values that are non-missing for both variables. In cases where the pairwise inverse is singular, the imputation algorithm instead uses minimum norm least squares imputation, based on the Moore-Penrose pseudo-inverse. Shrinkage estimation was used as part of this imputation procedure to improve the estimation of the covariance matrix. Comparison of the means and standard deviations of the affected variables generated before and after the imputation procedure revealed no significant differences, suggesting that imputation did not appreciably alter the characteristics of the data (Table 4).

*Estimation*

For Aim 1, path and structural equation models were generated via maximum likelihood estimation (MLE) with bootstrapping to account for the nonparametric distribution (Kline, 2011). As default MLE assumes multivariate normal distribution of data, the bootstrap procedure provides a resampling method that provides more accurate Type I error rates. Unbiased covariances were supplied as input, and maximum likelihood covariances were analyzed. Unstandardized estimates were generated for each path, and each path was tested for significance by dividing the sample estimate by the bootstrapped standard error.

For Aim 2, latent growth models were generated via maximum likelihood estimation (MLE). Bootstrapping was not used, given evidence that bootstrapping increases Type II error rates for sample sizes of 80 or fewer (e.g., Koopman et al., 2015). Unbiased covariances were supplied as input, and maximum likelihood covariances were analyzed. Unstandardized estimates were generated for each path, and each path was tested for significance by dividing the sample estimate by the sample standard error.

*Evaluation of Path Models*

Resulting path models were evaluated and respecified or retained based on the following criteria: (1) the model reasonably fits the data; (2) the model is reasonably parsimonious; and (3) the model is theoretically consistent (Kline, 2011). Further description of the first two criteria is provided below, while the third criterion is addressed on a model-by-model basis in the results and discussion.

**(1) The model reasonably fits the data.**

Models were assessed and compared using several fit indices.

**CMIN:** First, the model chi-square (or minimum chi-square, CMIN) is the traditional test for assessing overall model fit (Hooper, Coughlan, & Mullen, 2008). Also referred to as the discrepancy function, likelihood ratio chi-square, or chi-square goodness of fit, this test evaluates the size of the discrepancy between the sample and the fitted covariance matrices (Hu & Bentler, 1999). Good model fit is indicated by a nonsignificant result at the 0.05 threshold. This fit index has been largely considered to be overly conservative in many cases and, while still reported, is usually less informative than other fit indices.

**NFI:** The Normed-Fit Index (NFI; Bentler & Bonnet, 1980) compares the chi-square value of the model to the chi-square value of the null model, which specifies that all measured values are uncorrelated). NFI values range between 0 and 1, with values at or above .95 indicating good fit.

**TLI:** The Tucker Lewis Index (TLI; also known as the Non-Normed Fit Index, NNFI) is relatively independent of sample size. Acceptable fit is indicated by TFI values greater than .9, while good fit is indicated by values over .95. Values over .9 or .95 are acceptable.

**CFI:** The Comparative Fit Index (CFI; Bentler, 1990) is a revised form of the NFI that accounts for sample size. Like the NFI, the CFI assumes that all latent variables are uncorrelated, and compares the

sample covariance matrix with the null model. In other words, CFI can be interpreted as the percent of the covariation in the data that can be explained by the given model. CFI values range from 0 - 1, with values closer to 1 indicating good fit. Acceptable fit is indicated by values above .9, while good fit is indicated by CFI values equal to or greater than .95.

**RMSEA:** The Root Mean Square Error of Approximation (RMSEA; Steiger, 1990) indicates the degree to which the model (with unknown but optimally chosen parameter estimates) would fit the population's covariance matrix. Because of its sensitivity to the number of estimated parameters in the model, the RMSEA index has become regarded as 'one of the most informative fit indices' (Diamatopoulos & Siguaw, 2000; Hooper, Coughlan, & Mullen, 2008). General consensus (e.g., Hu & Bentler, 1999) suggests that good fit is indicated by RMSEA values close to or below .06.

**AIC:** Finally, the Akaike information criterion (AIC) is a measure of the relative quality of path models for a given dataset, taking into consideration both the goodness of fit and the model complexity. The AIC is calculated with following equation: $AIC = 2k - 2\ln(L)$, where the $k$ is the number of estimated parameters in the model, and $L$ is the maximum value of the likelihood function for the model. Founded in information theory, the AIC rewards goodness of fit but assigns a penalty that increases as the number of estimated parameters increases. The AIC provides a method for model selection when comparing non-nested models, with the preferred model being the one with the smallest AIC value.

**(2) The model is reasonably parsimonious**.

Models retained after application of the first criterion were then compared for parsimony. Specifically, the path coefficients for each model were evaluated for significance. Models without nonsignificant unstandardized estimates (i.e., *p*s >.05) were considered the most parsimonious.

***Aim 1***

*Construction of an Omnibus Aim 1 Model*

An omnibus path model of the hypothesized relationships between fatigue, RM, PM, CSU, and adherence was constructed to address some assumptions inherent to the initial data plan (Figure 1). The tested assumptions were as follows: (1) that fatigue, RM, and PM would show significant direct

relationships with adherence; (2) that fatigue would not be significantly associated with either retrospective or prospective memory; (3) that the three selected measures of adherence (i.e., the MEMS, BERMA MMES, and ACTG) would each contribute significantly to an adherence latent variable; and (4) that RM and PM would be modeled by the composite score calculations described earlier in a manner consistent with conceptual understanding of these constructs. The most statistically and theoretically appropriate adjustment of this model was then used as the foundation for addressing the Aim 1 hypotheses.

*Hypothesis 1*

A blended approach of alternative models testing and model generation was used to address the first hypothesis (i.e., that fatigue and memory impairment exert interaction effects on adherence). Four alternative model sets were generated: (H1A) that fatigue and memory each exert direct and independent effects on adherence; (H1B) that fatigue and memory interact to affect adherence; (H1C) that fatigue mediates the relationship between memory and adherence; and (H1D) that memory mediates the relationship between fatigue and adherence. Within each alternative model set, additional models were generated to reflect different aspects of the modeled relationships (e.g., that fatigue mediates the relationship between RM and adherence, but not PM; see Figure 6E), and respecified as needed to construct the most parsimonious and best-fitting versions of the models within each alternative model set. Retained alternative models for each set were then compared and evaluated using the criteria described above.

*Exploratory Hypothesis 2*

A similar approach was used to address the second hypothesis (i.e., whether fatigue and memory impairment affect adherence indirectly through CSU). Five alternative models were generated: (H2A) that fatigue, RM, PM, and CSU each only affect adherence directly; (H2B) that CSU mediates the relationships between fatigue and adherence; (H2C) that CSU mediates the relationships between memory and adherence; (H2D) that there is an interactive effect of fatigue and CSU on adherence; and (H2E) that there is an interactive effect of CSU and memory on adherence. Within each alternative model, additional

models were generated to reflect different aspects of the modeled relationships (e.g., that CSU mediates the relationship between RM and adherence, but not PM and adherence; see Figure 9E), and respecified as needed to construct the most parsimonious versions of the models within each alternative model set. Retained alternative models for each set were then compared and evaluated using the criteria described above.

*Covariate Hypothesis*

Finally, we tested the fit and parsimony of our final model against alternative models controlling for potential covariates of the effects of fatigue and memory on adherence. Additionally, as fatigue and depression are closely related, such that fatigue is sometimes conceptualized as a symptom of depression (e.g., Millikin, Rourke, Halman, & Power, 2002), an alternative model replacing fatigue with depressive symptomatology was also generated and compared to the final model (see Figure 14).

*Final Model Considerations*

**Adherence:** Given that the adherence latent variable was comprised of both an objective measure of adherence behavior (MEMS) and a measure of perceived efficacy of medication management (BERMA MMES), we sought to determine whether fatigue, strategy use, and memory impairment were differentially associated with perceived medication management efficacy than of objective medication taking-behavior. We predicted that, as perceptions of resource availability (fatigue) and medication management behavior (strategy use), fatigue and strategy use would be more strongly associated with perceived efficacy of medication management (BERMA MMES) than of objective medication taking-behavior (MEMS). We also predicted that memory impairment, as a more objective measure of resource availability, would be more strongly associated with objective medication taking-behavior (MEMS) than with perceived efficacy of medication management (BMMES).

These predictions were addressed using a blended approach of alternative models testing and model generation. Specifically, an alternative model was constructed of direct effects of fatigue, CSU, and RM/PM on each significant contributing variable to the adherence latent variable (i.e., MEMS and

BERMA MMES). This alternative model was respecified as needed to construct the most parsimonious version of the model, which was then compared to the Aim 1 final model (Figure 15).

**Prospective memory:** Given prior data investigating the relative effects of 2-minute and 15-minute delay intervals on the relationship between PM and adherence (Poquette et al., 2013), we sought to explore whether participant performances on the MIST 15-minute and 24-hour subtests would be differentially associated with adherence and with the rest of the model. To test these considerations, we constructed alternative models by replacing the PM latent variable with either the MIST 15-minute or the MIST 24-hour subscale scores, and compared the fits of the alternative models to the Aim 1 final model (Figure 16).

***Aim 2***

All Aim 2 hypotheses were addressed using latent growth modeling. Latent growth models were constructed by creating latent variables of the intercepts and slopes for each experimental variable. For each variable, the intercept was regressed to the variable at both time points with a fixed regression weight of 1. The slope was regressed to the variable at time 1 at a fixed regression weight of 0, and regressed to the variable at time 2 at a fixed regression weight of 0. Regression weights for residual errors were fixed at 1 for all variables, and were assumed to be uncorrelated. Residual error variances were fixed to 0 for all time-2 variables, but left free for all time-1 variables. Intercepts and slopes of all variables in the model were tested for significant covariances. For all Aim 2 models, measurement of compensatory strategy use (CSU) was shifted from PMMQ total scores to PMMQ percent use scores, which reflect the number of strategies employed by participants but not the frequency at which they were utilized. Thus, for all Aim 2 models, CSU was described as "CSU number" rather than "CSU frequency."

*Hypotheses 3 and 4*

Hypothesis 3 (i.e., that change in fatigue would be significantly associated with change in perceived medication management efficacy) was addressed by building two individual latent growth models: one for fatigue, and one for perceived efficacy. The intercepts and slopes of each latent growth model were tested for significant covariances. The same model design was used to address Hypothesis 4

(i.e., that change in CSU number would be significantly associated with change in perceived medication management efficacy).

*Hypothesis 5*

To address Hypothesis 5 (i.e., that changes in RM and PM would be significantly associated with change in perceived medication management efficacy), three alternative latent growth models were generated. The first two models were comprised of an individual latent growth model for perceived efficacy and in individual latent growth model for either RM (1), or for PM (2). The third model was comprised of three individual latent growth models, one each for RM, PM, and perceived efficacy. For all models, the intercepts and slopes of each latent growth model were tested for significant covariances. Models were respecified as needed to construct the most parsimonious versions of the models.

*Hypothesis 6*

Finally, to test Hypothesis 6 (i.e., that the data would be best fit by a model of the associations between changes in fatigue, CSU number, and perceived efficacy), a model was constructed of three individual latent growth models: one each for fatigue, CSU number, and perceived efficacy. The intercepts and slopes of each latent growth model were tested for significant covariances, and the fit indices of the model were compared to those of the other Aim 2 models to assess the best-fitting model.

# RESULTS

## Missing Value Analysis

### *Baseline Cohort*

Among the clinicodemographic variables, less than one percent of participant data was missing for current/lifetime diagnoses of generalized anxiety disorder (Table 1). Across the HIV infection and treatment variables, fewer than five percent of participants were missing data for nadir and current CD4 T-cell counts, plasma HIV RNA, and current cART regimens, while 8.5 percent of data were missing for estimated duration of HIV infection (Table 2). No other data were missing for all other clinicodemographic or medical variables. Among the experimental variables, fewer than five percent of data points were missing for the CVLT-II, the BERMA MMES, and ACTG, while nine percent of participants were missing data for the PMMQ (Table 3). No other data were missing from the other experimental variables. Careful examination of the array of missing data points reflected a largely random pattern of missing data, with none of the participants missing more than two data points (Table 5). Eleven participants were missing data for both duration of HIV infection and the PMMQ; however, only the PMMQ was included in subsequent path analysis, which eliminated the possibility that this pattern of missing data would affect the results.

### *Longitudinal Cohort*

No clinicodemographic data points were missing at baseline (Table 6). At one-year follow-up, fewer than five percent of participants were missing data for current diagnosis of substance use disorders; no other clinicodemographic data were missing. Across the HIV infection and treatment variables at baseline, fewer than five percent of data were missing for nadir and current CD4 T-cell counts (Table 7). At follow-up, fewer than five percent of participants were missing data for plasma HIV RNA, while 5.3 percent of participants (N=3) were missing data for current cART regimens. No other data points were missing for the medical variables at either time point. No experimental data were missing at baseline (Table 8). Among the experimental variables at follow-up, fewer than five percent of data points were missing for PMMQ, CVLT-II, LM II, and MIST 24-hr. No other data were missing from the other

experimental variables. ACTG and MEMS data were not used in longitudinal analyses. Careful examination of the array of missing data points reflected a largely random pattern of missing data, with none of the participants missing more than two data points (Table 9).

**Aim 1**

***Omnibus Model Construction***

The omnibus model (Figure 1) represented the direct relationships between fatigue, RM, PM, and cART adherence, with indirect effects of the former variables on adherence through CSU. All parameter estimates were identified, and model fit indices indicated excellent fit of the omnibus model to the data ($\chi^2$=9.846, *df*=8, *p*=.276; NFI=.941; TLI=.967; CFI=.987; RMSEA=.036). As expected, fatigue (unstandardized $\gamma_{a.fat}$= -.43, *p*=.0027), and the RM (unstandardized $\gamma_{a.rmz}$=1.81, *p*=.029) and PM (unstandardized $\gamma_{a.pmz}$=2.26, *p*=.017) composite scores all demonstrated significant direct relationships with adherence. Additionally, fatigue was not significantly related to RM ($r_{rmz,fat}$= -.15, *p*=.72) or PM ($r_{pmz,fat}$= -.03, *p*=.93).

While BERMA MMES and MEMS scores were found to be significant contributors to the adherence latent variable (Figure 1: $\lambda_{adh.b}$=1.59, *p*=.020, with $\lambda_{adh.m}$ set to 1.00 to scale the latent variable; standardized factor loadings were $\lambda_{adh.b}$=.85, *p*=.039; and $\lambda_{adh.m}$=.31, *p*<.001), the path for the contribution of ACTG to the adherence latent variable was nonsignificant (unstandardized $\lambda_{adh.a}$=.05, *p*=.48). The omnibus model was respecified by dropping ACTG from the adherence latent variable and entering it as a separate endogenous variable, thus adding three additional paths (Figure 2B). Though all parameter estimates were identified, and all five model fit indices indicated acceptable fit ($\chi^2$=2.263, *df*=5, *p*=.812; NFI=.987; TLI=.1.076; CFI=1; RMSEA=0), unstandardized parameter estimates of the relationships between the exogenous variables and ACTG were either nonsignificant ($\gamma_{a,pmz}$=1.09, *p*=.058; $\gamma_{a.rmz}$= -.18, *p*=.61; $\gamma_{a.csu}$= -.04, *p*=.058) or quite small ($\gamma_{a.fat}$=.09, *p*=.048). Accordingly, ACTG was dropped from the respecified model (e.g., Figure 2C) and all subsequent models. This respecified model retained acceptable fit indices in the absence of ACTG ($\chi^2$=1.965, *df*=3, *p*=.580; NFI=.988; TLI=.1.035; CFI=1; RMSEA=0),

and demonstrated the most balance between complexity and goodness of fit of the three models (i.e., $AIC_{2A}$=63.85; $AIC_{2B}$=62.26; $AIC_{2C}$=49.97).

We then considered the statistical implications of using composite scores for RM and PM. The primary concern was that calculation of composite scores "traps" unobserved error into the composite. Due to this inability to separate error from the composite scores, path analysis with these scores could be confounded by the trapped error and cause misrepresentation of findings. In response, the first respecification of the model was conducted by entering the raw scores of the four memory measures (i.e., CVLT-II, LM II, MIST 15-min, and MIST 24-hr) into a single memory latent variable (see Figure 3B). Model fit indices indicated good fit ($\chi^2$=20.68, *df*=16, *p*=.191; NFI=.914; TLI=0.962; CFI=.978; RMSEA=.041). All four memory measures contributed significantly to the memory latent variable ($\lambda_{mem.l}$=6.86, *p*<.001; $\lambda_{mem.c}$=2.83, *p*<.001; $\lambda_{mem.24}$=.33, *p*<.001; with $\lambda_{mem.15}$ set to 1.00 to scale the latent variable; standardized factor loadings were $\lambda_{mem.l}$=.73, $\lambda_{mem.c}$=.68 $\lambda_{mem.24}$=.39, and $\lambda_{mem.15}$=.52, with all *p*s<.001), which evidenced a significant direct effect on adherence ($\gamma_{adh.mem}$=3.2, *p*=.0047).

However, as evidence from prior literature (e.g., Woods et al., 2008b) suggests that RM and PM have dissociable effects on adherence, this respecified model was determined to be less conceptually accurate than the omnibus model. Instead, the model was again respecified, with RM and PM included in the model as two separate latent variables (see Figure 3C). The MIST 15-minute and 24-hour raw scores were included as indicators for the PM latent variable, and the CVLT-II and LM II delayed recall raw scores were included as indicators for the RM latent variable. All parameter estimates of this new model were identified, and model fit indices indicated acceptable fit ($\chi^2$=16.871, *df*= 12, *p*=.155; NFI=.930; TLI=.947; CFI=.977; RMSEA=.048). Respecification of the model to remove the nonsignificant effects of RM and PM on CSU (Figure 3D) and again to remove nonsignificant correlations between RM and fatigue, and between PM and fatigue (Figure 3E) resulted in increasingly improved model fit indices (Figure 3D: $\chi^2$=16.833, df= 14, p=.265; NFI=.932; TLI=.974; CFI=.987; RMSEA=.034. Figure 3E: $\chi^2$=17.089, df= 16, p=.380; NFI=.931; TLI=.991; CFI=.995; RMSEA=.02). in the resultant model (Figure 3E), each of the PM measures contributed significantly to the PM latent variable (unstandardized

$\lambda_{pml.15}$=3.145, *p*=.0022, with $\lambda_{pml.24}$ set to 1.00 to scale the latent variable; standardized factor loadings were $\lambda_{pml.15}$=.55, *p*<.001; $\lambda_{pml.24}$=.40, *p*<.001) and each of the RM measures contributed to the RM latent variable ($\lambda_{rml.l}$=2.44, *p*<.001with $\lambda_{rml.c}$ set to 1.00 to scale the latent variable; standardized factor loadings were $\lambda_{rml.l}$=.75, *p*<.001; $\lambda_{rml.c}$=.70, *p*<.001). The model also revealed significant effects of fatigue (unstandardized $\gamma_{a.fat}$= -0.43, *p*=.0039) and strategy use (unstandardized $\gamma_{a.csu}$= -0.17, *p*=.01) on adherence. However, these respecification steps did not produce significant estimates for the effects of RM and PM on adherence (Figure 3E: unstandardized $\gamma_{adh.pml}$=21.19, *p*=.37; $\gamma_{adh.rml}$= -1.18, *p*=.66).

Final respecification of the model was conducted by removing one of the two remaining nonsignificant estimates for the effects of RM and PM on adherence. The first model removed the relationship between RM and adherence (Figure 3F), while retaining the estimated relationship between PM and adherence, and the RM latent variable as a covariate of the effects of PM on adherence. The model was identified, and model fit indices indicated improved fit over the other models retaining RM and PM as latent variables ($\chi^2$=17.594, *df*= 17, *p*=.415; NFI=.929; TLI=.996; CFI=.997; RMSEA=.014). The second model removed the relationship between PM and adherence (Figure 3G), while retaining the estimated relationship between RM and adherence, and the PM latent variable as a covariate of the effects of RM on adherence. This second model was also identified, and model fit indices indicated acceptable fit indices ($\chi^2$=21.341, *df*= 17, *p*=.211; NFI=.913; TLI=.967; CFI=.98; RMSEA=.038). However, the first model, 3F, was a better fit of the data, given the smaller RMSEA (i.e., .014 vs. .038) and AIC ($AIC_{3F}$=71.594 vs. $AIC_{3G}$=75.341).

To assess for parsimony, Model 3F was respecified to remove RM completely (Figure 3H). The resultant model was identified, with acceptable fit indices ($\chi^2$=11.217, *df*= 7, *p*=.129; NFI=.918; TLI=.925; CFI=.965; RMSEA=.059), and was more parsimonious than Model 3F (3H AIC=51.217 vs. 3F AIC=71.594). However, comparison of the fit indices indicated that Model 3H was a less appropriate fit of the data than Model 3F, as Model 3H had a much larger RMSEA (.059 vs. .014), and smaller TLI (.925 vs. .996), which also fell below the .95 threshold. Furthermore, the effect of PM on adherence lost significance with the removal of RM (3H: unstandardized $\gamma_{a.pml}$=12.52, *p*=.25).

Taken together, these initial analyses suggested that: (1) the effect of fatigue on adherence (whether direct or indirect) is independent from that of memory; (2) fatigue was not significantly associated with RM or PM; (3) the adherence latent variable was most parsimoniously represented by contributions from the BERMA MMES and MEMS scores; and (4) from a conceptual standpoint, memory was best modeled by RM and PM latent variables.

***Hypothesis 1***

To address the first hypothesis (i.e., that fatigue and memory impairment exert an interaction effect on adherence), four sets of alternative models were generated.

*Hypothesis 1A: Direct Effects*

The first model set addressed whether the data would be fit better by a model comprised of only direct and independent effects of fatigue, RM, and PM on adherence, without contributions from CSU (Figure 4). The initial model (Figure 4A) included direct relationships between adherence and fatigue, RM, and PM. As fatigue was not expected to be significantly associated with either RM or PM, based on the results of the omnibus model analyses (see Figures 3C and 3D), only the correlation between RM and PM was included in the model. This model was identified and evidenced acceptable fit ($\chi^2$=7.992, *df*=11, *p*=0.714; NFI=.959; TLI=1.033; CFI=1; RMSEA=0); however, the factor loading for the contribution of BERMA MMES to the adherence latent variable was nonsignificant (4A: $\lambda_{adh.b}$=2.03, *p*=.18), and neither RM (unstandardized $\gamma_{adh.rml}$= -.62, *p*=.78) nor PM (unstandardized $\gamma_{adh.pml}$=14.74, *p*=.51) retained significant relationships with adherence. The model was respecified by either removing the path between RM and adherence (Figure 4B) or by removing the path between PM and adherence (Figure 4C). Both respecified models were identified. Neither model retained significant factor loadings for the contribution of BERMA MMES to the adherence latent variable (4A: $\lambda_{adh.b}$=2.03, *p*=.18; 4B: $\lambda_{adh.b}$=2.04, *p*=.078; 4C: $\lambda_{adh.b}$=2.07, *p*=.18). As such, none of the models of this set were selected for consideration as a best-fitting model.

*Hypothesis 1B: Interaction Effects of Fatigue and Memory*

The second model set addressed whether the data would be fit better by a model comprised of interactive effects of memory and fatigue on adherence (Figure 5). Interaction effects were constructed by including the product constants of the fatigue and memory variables as latent variables, one for the interaction between RM and fatigue (i.e., FRM, comprised of the CVLT-II/POMS-FI and the LM II/POMS-FI product constants) and one for the interaction between PM and fatigue (i.e., FPM, comprised of the MIST 15-minute/POMS-FI and the MIST 24-hour/POMS-FI product constants). The initial model (Figure 5A) was comprised of direct effects of fatigue, RM, and PM on adherence, as well as interaction effects of fatigue/RM and fatigue/PM on adherence. Covarying relationships were included between RM and PM and between the interaction terms. The model was identified but fit the data poorly, as evidenced by model fit indices that did not meet appropriate thresholds ($\chi^2$=62.4, *df*=38, *p*=0.008; NFI=.842; TLI=.896; CFI=.928; RMSEA=.060). Respecification of the model to isolate the interaction effect between PM and fatigue on adherence (Figure 5B), or the interaction effect between RM and fatigue on adherence (Figure 5C) did not improve the fit of the model (5B: $\chi^2$=65.21, *df*=40, *p*=0.007; NFI=.835; TLI=.898; CFI=.926; RMSEA=.060. 5C: $\chi^2$=68.66, *df*=40, *p*=0.003; NFI=.826; TLI=.884; CFI=.916; RMSEA=.064). Thus, none of the models of this set were selected for consideration as a best-fitting model.

*Hypothesis 1C: Fatigue as a Mediator*

The third model set addressed whether the data would be fit better by a model reflecting fatigue as a mediator of the effects of RM and PM on adherence (Figure 6). Construction of the initial model (Figure 6A) included direct paths from RM and PM to adherence and indirect paths from RM and PM through fatigue to adherence. RM and PM were also expected to covary. The initial model was identified and evidenced appropriate model fit indices ($\chi^2$=7.688, *df*=9, *p*=.566; NFI=.961; TLI=1.018; CFI=1; RMSEA=0). However, the unstandardized estimates of the effects of RM and PM on fatigue were non-significant ($\gamma_{fat.rml}$= -.11, *p*=.93; $\gamma_{fat.pml}$= -.12, *p*=.99). A series of respecifications of the model to isolate the mediation effect of fatigue on the relationship between PM and adherence (Figures 6B and 6C) or on the relationship between RM and adherence (Figures 6D and 6E) also failed to retain significant

unstandardized estimates of the effects of PM or RM on fatigue (6B: $\gamma_{fat.pml}$= -1.16, *p*=.67; 6C: $\gamma_{fat.pml}$= -1.14, *p*=.67; 6D: $\gamma_{fat.rml}$= -.13, *p*=.61; 6E: $\gamma_{fat.rml}$= -.11, *p*=.63). Thus, none of the models of this set were selected for consideration as a best-fitting model.

*Hypothesis 1D: Memory as a Mediator*

The final model set addressed whether the data would be fit better by a model including RM and PM as mediators of the effects of fatigue on adherence. Construction of the initial model (Figure 7A) included a direct path from fatigue to adherence, as well as indirect paths from fatigue through RM and PM to adherence. The initial model was identified, but fit the data poorly, as evidenced by significant chi-square results and model fit indices that did not meet appropriate thresholds ($\chi^2$=46.434, *df*=10, *p*<.001; NFI=.762; TLI=.56; CFI=.791; RMSEA=.144). Respecifications of the model to include only PM (Figure 7B) or only RM (Figure 7C) as a mediator of the relationship between fatigue and adherence resulted in improved model fit indices (7B: $\chi^2$=1.392, *df*=3, *p*=.707; NFI=.984; TLI=1.07; CFI=1; RMSEA=0. 7C: $\chi^2$=4.673, *df*=3, *p*=.197; NFI=.965; TLI=.955; CFI=.986; RMSEA=.056); however, the respecified models failed to retain significant unstandardized estimates of the effect of fatigue on PM (7B: $\gamma_{pml.fat}$= -.002, *p*=.69) or RM (7C: $\gamma_{rml.fat}$= -.017, *p*=.72). Consequently, none of the models of this set were selected for consideration as a best-fitting model.

*Hypothesis 1 Summary*

The data were not best fit by a model comprised of only direct, independent effects of fatigue and memory impairment on adherence (Figure 4). Alternate model sets hypothesizing an interactive effect of fatigue and memory impairment on adherence (Figure 5), or mediating relationships between fatigue and memory impairment on adherence (Figure 6 and 7), either evidenced poor model fit or failed to retain significant unstandardized estimates of the expected relationships.

***Exploratory Hypothesis 2***

To address the second hypothesis (i.e., whether fatigue and memory impairment affect adherence both directly and indirectly through CSU), five alternative model sets were generated.

*Hypothesis 2A: Direct Effects*

The first model set addressed whether the data would be fit better by a model comprised of direct effects of fatigue, CSU, RM, and PM on adherence (Figure 8A). All possible correlations were included between the exogenous variables, as CSU had not been included previously as an exogenous variable. The model was identified and evidenced acceptable model fit indices ($\chi^2$=16.731, *df*=12, *p*=.16; NFI=.932; TLI=.949; CFI=.978; RMSEA=.047). Respecification of the model through removal of non-significant correlations (Figure 8B) resulted in an identified model with improved fit indices ($\chi^2$=17.089, *df*=16, *p*=.38; NFI=.931; TLI=.991; CFI=.997; RMSEA=.02) and significant unstandardized estimates of the effects of fatigue and CSU on adherence ($\gamma_{adh.fat}$= -.43, *p*=.0039; $\gamma_{adh.csu}$= -.17, *p*=.010); however, the effects of RM and PM on adherence remained non-significant ($\gamma_{adh.rml}$= -1.18, *p*=.66; $\gamma_{adh.pml}$=21.19, *p*=.37). The model was further respecified by removing either the effect of RM on adherence (Figure 8C), or the effect of PM on adherence (Figure 8D). In both cases, the remaining effect of memory on adherence retained significance (8C: $\gamma_{adh.pml}$=10.58, *p*=.020; 8D: $\gamma_{adh.rml}$= 1.14, *p*=.007). Comparison of model fit indices across all four models revealed Figure 8C fit the data best, and was thus retained for best-fit comparison.

*Hypothesis 2B: CSU as a Mediator of Fatigue and Adherence*

The models that comprised this second model set were identical to some of those featured in the analyses of the omnibus model; see Figures 3E, 3F, and 3G, and the relevant sections above for fit values and other details. In brief, the model was constructed with direct path estimates from fatigue, RM, PM, and CSU to adherence, as well as a path estimate from fatigue to CSU (Figure 3E). The model was identified and evidenced acceptable model fit indices. While the standardized path estimates from fatigue and CSU to adherence were significant, as well as the standardized path estimate from fatigue to CSU, the path estimates from RM and PM to adherence remained nonsignificant. Respecification of the model by removing the path from RM to adherence (Figure 3F) or by removing the path from PM to adherence (Figure 3G) produced identified models with acceptable fit indices and significant unstandardized estimates between all variables. Comparison of the fit indices and AIC values between Figure 3F and

Figure 3G showed that Figure 3F was a significantly better fit to the data. Thus, Figure 3F was retained as the best-fitting model of this set.

*Hypothesis 2C: CSU as a Mediator of Memory and Adherence*

The third model set addressed whether the data would be fit better by a model including CSU as a mediator of the relationship between memory and adherence (Figure 9). The initial model was constructed with paths from fatigue, CSU, RM, and PM to adherence, and paths from RM and PM to CSU (Figure 9A). This model was identified, but evidenced poor model fit indices, including significant chi-square results and model fit indices that did not meet acceptable thresholds. Model fit was not improved by respecification of the model to isolate the mediating effect of CSU on the relationship between PM and adherence (Figure 9B) or RM and adherence (Figure 9D), even when the effect of RM on adherence (Figure 9C) or PM on adherence (Figure 9E) was removed from the model. Consequently, none of these models were retained for consideration as a best-fitting model.

*Hypothesis 2D: Interaction Effects of CSU and Fatigue*

The fourth model set addressed whether the data would be fit better by a model including an interaction effect of fatigue and CSU on adherence (Figure 10). The initial model was constructed of paths from fatigue, CSU, FCS (the fatigue/CSU product constant), RM, and PM to adherence, and included all potential covariances (Figure 10A). The model was identified and evidenced acceptable model fit indices ($\chi^2$=20.33, *df*=15, *p*=0.16; NFI=.92; TLI=.941; CFI=.976; RMSEA=.045). Respecification of the model to remove non-significant covariances (Figure 10B) and removal of the effect of RM (Figure 10C) or PM (Figure 10D) on adherence failed to result in a significant effect of the fatigue/product constant on adherence. Thus, none of the models were retained for best-fit analysis.

*Hypothesis 2E: Interaction Effects of CSU and Memory*

The final model set addressed whether the data would be fit better by a model that included interaction effects of memory and CSU on adherence (Figure 11). Interaction effects were constructed in a similar manner to that employed for the H1B models (Figure 5). The initial model was constructed of direct path estimates from fatigue, CSU, CSRM (the CSU/RM product constant), CSPM (the CSU/PM

product constant), RM, and PM, and included all potential covariances (Figure 11A). The model was identified and evidenced acceptable model fit indices ($\chi^2$=37.91, *df*=35, *p*=0.338; NFI=.909; TLI=.983; CFI=.991; RMSEA=.022). Respecification of the model to remove nonsignificant covariances (Figure 11B) and then to isolate the interaction between CSU and PM (Figures 11C and 11E) or between CSU and RM (Figures 11D and 11F) failed to produce a model in which an interaction between CSU and memory evidenced a significant effect on adherence. Consequently, none of the models were retained for best-fit analysis.

***Best-Fit Analysis***

Across all Hypothesis 1 and 2 model sets, only models including direct estimates of the effects of fatigue, CSU, and PM on adherence, and either a mediating (Figure 3F) or covarying (Figure 8C) relationship between fatigue and CSU, were retained for consideration as best-fitting models. In contrast, models comprised of other mediating or moderating relationships between fatigue, CSU, RM, and PM either evidenced poor model fit, or failed to retain significant unstandardized estimates of the expected relationships.

To determine which of the two remaining models represented the best fit of the data, a third alternative model was generated to consider the relative fit of a mediating effect of fatigue on the relationship between CSU and adherence (Figure 12A). This model was identified, evidenced fit indices that were identical to that of the other two retained models, and did not reflect any nonsignificant estimates or factor loadings. To tease out the relative fits of the mediation models (Figures 3F and 12A), a fourth model was constructed to attempt to model the relative effects of fatigue and CSU on one another (Figure 12B). However, the model was not recursive and thus could not be identified.

Given the identical model fit indices across the three models (Figures 3F, 8C, and 12A), the difficulty in determining causation within cross-sectional data supported the selection of Figure 8C as the best-fitting model of the data for Aim 1.

***Covariate Hypothesis***

*Selection of Covariates*

Likely covariates were selected using both theoretical and data-driven considerations. Prior evidence has supported strong relationships between adherence and age (e.g., Barclay et al., 2007) and depression (e.g., Gonzalez et al., 2011). Pill burden was also considered, as a recent study from our lab found that pill burden influences the relationship between time-based PM and adherence among younger adults with HIV (Sheppard et al., 2016). In the current study, age was significantly related to BERMA MMES scores ($r_s$=-.180, *p*=.017), as well as MIST 15-minute ($r_s$=-.368, *p*<.0001) and PMMQ ($r_s$=.227, *p*=.004) scores. Self-reported depressive symptomatology (i.e., POMS-DD) was significantly related to BERMA MMES ($r_s$=-.467, *p*<.0001), as well as fatigue ($r_s$=.589, *p*<.0001), MIST 15-minute ($r_s$=-.168, p=.025), and LM II ($r_s$= -.251, *p*=.0008) scores. Overall pill burden was significantly related to BERMA MMES scores (F=12.7, *p*=.0005), as well as fatigue (F=24.5, *p*<.0001), MIST 15-minute (F=6.78, *p*=.010), and LM II (F=5.58, *p*=.019) scores.

Finally, HAND diagnosis was considered as a potential covariate to assess the possibility that the interrelationships observed in the best-fitting Aim 1 model could reflect the overall presence and severity of HAND. However, because the HAND diagnosis was extremely skewed in the current study (skew index = 17.35, well above the 3.0 threshold suggested by Kline, 2011), global clinical rating score was included as a covariate instead to assess the effects of general level of cognitive ability on the interrelationships of the other variables in the best-fitting Aim 1 model. Global clinical rating score was significantly related to the BERMA MMES (F=4.5, *p*=.0353), MIST 15-minute (F=15.40, *p*<.0001), MIST 24-hour (F=6.50, *p*=.0116), CVLT-II (F=32.85, *p*<.0001), and LM II (F=24.45, *p*<.0001) scores.

*Covariate Model Construction and Best-Fit Analysis*

A test of age, pill burden, and depressive symptomatology as covariates of the best-fitting model from Hypotheses 1 and 2 (Figure 8C) was constructed into one model (Figure 13B). The model was identified and evidenced acceptable model fit indices ($\chi^2$=34.587, *df*=26, *p*=.121; NFI=.924; TLI=.955; CFI=.979; RMSEA=0.043). Respecification of the model to remove nonsignificant covariances (Figure 13C) produced a model with worse fit indices (e.g., $\chi^2$=50.167, *df*=32, *p*=.021). The respecified model also evidenced nonsignificant unstandardized estimates of the effects of age and pill burden on adherence

($\gamma_{adh.age}$=.073, *p*=.25; $\gamma_{adh.bur}$=.097, *p*=.6), while the effect of depressive symptomatology on adherence was significant ($\gamma_{adh.dep}$= -.13, *p*=.047). Respecification of the model by removing age as a covariate (Figure 13D) resulted in a model with improved fit indices ($\chi^2$=32.324, *df*=26, *p*=.183; NFI=.919; TLI=.969; CFI=.982; RMSEA=0.037), but the effect of pill burden on adherence remained nonsignificant ($\gamma_{adh.bur}$=.155, *p*=.36). Alternate respecification of the model by removing pill burden as a covariate (Figure 13E) did not produce improved fit indices (e.g., $\chi^2$=46.169, *df*=28, *p*=.017). Finally, alternate respecification of the model by removing depression as a covariate (Figure 13I) resulted in a model with improved fit indices ($\chi^2$=33.383, *df*=24, *p*=.096; NFI=.907; TLI=.944; CFI=.970; RMSEA=0.047), but the effects of age and pill burden remained nonsignificant ($\gamma_{adh.age}$=.104, *p*=.143; $\gamma_{adh.bur}$=.112, *p*=.568). Similarly, alternative models including age (Figure 13G) or pill burden (Figure 13H) as the sole covariate did not result in a significant effect of age on adherence (13G: $\gamma_{adh.age}$=.123, *p*=.083; 13H: $\gamma_{adh.bur}$=.193, *p*=.281). Finally, alternative models including global clinical rating scale as the sole covariate did not result in a significant effect of cognitive impairment on adherence (13J: $\gamma_{adh.gcr}$=.492, *p*=.448), even when the model was respecified by removing all non-significant covariances from the model (13K: $\gamma_{adh.gcr}$=.49, *p*=.436).

Final respecification of the model was achieved by removing both age and pill burden as covariates and retained (Figure 13F), the effect of depressive symptomatology on adherence with covariances between depressive symptomatology and fatigue, and between depressive symptomatology and RM. Compared to the other respecifications, this model evidenced the best fit indices, smallest AIC, and retained all significant unstandardized estimates and factor loadings (see Figure 13 for all numbers).

Best-fit analysis of the final covariate model (Figure 13F) and the Aim 1 final model (Figure 8C) revealed that the final Aim 1 model evidenced better fit indices (e.g., RMSEA =.014 (8C) vs. .036 (13F)) and smaller AIC (i.e., 71.594 (8C) vs. 90.984 (13F)) suggesting that the Aim 1 final model is ultimately a better fit of the data.

To determine whether depressive symptomatology better explains the role of fatigue in the Aim 1 final model, fatigue was removed from the model and replaced with depressive symptomatology (Figure

14B). Due to poor fit indices of the initial model (e.g., $\chi^2$=29.247, *df*=17, *p*=.032), the model was respecified to reflect the significant covariances between depressive symptomatology and the other variables in the model, as reflected by the earlier covariate analyses (e.g., Figure 13F). This respecified model (Figure 14C) evidenced improved model fit indices over that of the initial model, but similar to Figure 13F, evidenced poorer fit indices (e.g., RMSEA =.052 (14C) vs. .014 (8C)) and larger AIC (i.e., 79.168 (14C) vs. 71.594 (8C)) than the final Aim 1 model.

***Final Model Considerations***

*Adherence*

To determine whether fatigue, strategy use, and memory impairment were differentially associated with perceived medication management efficacy and with objective medication taking-behavior, one alternative model was generated. The model was constructed by removing the adherence latent variable, and by entering MEMS and BERMA MMES as separate endogenous variables, thus adding three additional paths (Figure 15). All parameter estimates were identified, and the model fit indices indicated acceptable fit ($\chi^2$=15.71, *df*=15, *p*=.402; NFI=.936; TLI=.994; CFI=.997; RMSEA=.016), with values very close to those of the final Aim 1 model. While all of the unstandardized parameter estimates of the relationships between the exogenous variables and BERMA MMES were significant, none of the unstandardized parameter estimates of the relationships between the exogenous variables and MEMS were significant ($\gamma_{mems,fat}$=.012, *p*=.96; $\gamma_{mems.csu}$= -.211, *p*=.073; $\gamma_{mems.pml}$=7.147, *p*=.42). Respecification of the model through removal of MEMS worsened the fit of the model ($\chi^2$=15.247, *df*=12, *p*=.228; NFI=.934; TLI=.973; CFI=.984; RMSEA=.039). Alternate respecification of the model through removal of BERMA MMES also worsened the fit of the model ($\chi^2$=14.672, *df*=12, *p*=.260; NFI=.901; TLI=.963; CFI=.979; RMSEA=.036), though it revealed a significant effect of CSU frequency on MEMS ($\gamma_{mems.csu}$= -.188, *p*=.006). Together, these data indicate that while fatigue, PM, and strategy use have direct significant associations with BERMA MMES, but not MEMS when both are included separately in the model, the data were best fit by a model incorporating both BERMA MMES and MEMS as contributors to an adherence latent variable (i.e., the Aim 1 final model).

*Prospective Memory*

To determine whether delay interval affected the observed relationship between PM and adherence, two alternative models were generated by replacing the PM latent variable with either the MIST 15-minute (Figure 16B) or the MIST 24-hour (Figure 16C) subscale scores in the Aim 1 final model. The 15-minute delay alternative model was identified and evidenced acceptable model fit indices (i.e., $\chi^2$=19.175, *df*=12, *p*=.084; NFI=.912; TLI=.936; CFI=.963; RMSEA=.058). However, this model evidenced worse model fit than the Aim 1 final model (e.g., 16B RMSEA=.058 vs. final model RMSEA=.014). In contrast, the 24-hour delay alternative model was identified, but did not did not meet appropriate thresholds (i.e., $\chi^2$=29.273, *df*=12, *p*=.004; NFI=.856; TLI=.834; CFI=.905; RMSEA=.09), suggesting that the model was a poor fit to the data. Together, these data indicated that PM performance on the 15-minute delay subtests better explained the role of PM in the final model than PM performance on the 24-hour delay subtest, however, PM was best represented by both measures as contributors to a PM latent variable.

***Aim 1 Summary***

Best-fit analyses, covariate analyses, and post hoc analyses all supported selection of the model reflecting direct and covarying effects of fatigue and CSU frequency on adherence, and a direct and independent effect of PM, covaried with RM, on adherence as the best-fitting Aim 1 model (Figure 17). Adherence was most parsimoniously represented by a latent variable with contributions from the BERMA MMES and MEMS. RM and PM were represented by latent variables comprised of the CVLT-II and LM II delayed free recall raw scores (for RM) and the MIST 15-minute and MIST 24-hour subscale raw scores (for PM). Unstandardized estimates, covariances, and means for the Aim 1 final model are presented in Table 10.

**Aim 2**

***Hypothesis 3***

To address the third hypothesis (i.e., that change in fatigue would be associated with perceived efficacy to manage medications), a model was constructed of a latent growth model of fatigue and a latent

growth model of BERMA MMES, with covariances between their intercepts and slopes (Figure 18). The model was identified, but did not did not meet appropriate thresholds (i.e., $\chi^2$=5.615, *df*=2, *p*=.06; NFI=.941; TLI=.878; CFI=.959; RMSEA=.180), suggesting that the model was a poor fit to the data.

***Hypothesis 4***

To address the fourth hypothesis (i.e., that change in CSU number would be associated with change in perceived efficacy) a model was constructed of a latent growth model of CSU number and a latent growth model of BERMA MMES, with covariances between their intercepts and slopes (Figure 19). The model was identified and met appropriate thresholds (i.e., $\chi^2$=1.429, *df*=2, *p*=.489; NFI=.985; TLI=1.020; CFI=1.000; RMSEA=.000). Additionally, this model revealed significant covariances between CSU number and BERMA MMES between both their intercepts (cov(I-csu,I-bmmes)= -1.401, *p*<.001), and slopes (cov(S-csu,S-bmmes)= -.676, *p*=.017), supporting Model 19 as a candidate for best-fit analyses.

***Hypothesis 5***

To address the fifth hypothesis (i.e., that changes in RM and PM would be associated with changes in perceived efficacy), three alternative models were constructed. The first model was constructed of latent growth models of the RM latent variable and BERMA MMES, with covariances between their intercepts and slopes (Figure 20A). The model was identified, but did not did not meet appropriate thresholds (i.e., $\chi^2$=26.225, *df*=9, *p*=.002; NFI=.773; TLI=.714; CFI=.828; RMSEA=.185), indicating poor fit to the data. The second model, constructed of latent growth models of the PM latent variable and BERMA MMES, evidenced significantly better model fit (Figure 20B: $\chi^2$=10.059, *df*=9, *p*=.346; NFI=.821; TLI=.957; CFI=.974; RMSEA=.046). However, the MIST 24-hour scores did not contribute significantly to the PM latent variables at either time point (unstandardized $\lambda_{pml.24\text{-}t1}$= -.07, *p*=.626; and unstandardized $\lambda_{pml.24\text{-}t2}$= -.001, *p*=.983, with $\lambda_{pml.15\text{-}t1}$ and $\lambda_{pml.15\text{-}t2}$ set to 1.00 to scale the latent variables). The model was respecified by removing the MIST 24-hour scores, leaving the MIST 15-minute scores as an independent latent growth model (Figure 20C). The respecified model was identified and met appropriate thresholds ($\chi^2$=0.037, *df*=2, *p*=.982; NFI=.999; TLI=1.148; CFI=1.000;

RMSEA=.000). MIST-15 and BERMA MMES significantly covaried at baseline (cov(I-15,I-bmmes)= 6.146, *p*=.007), but changes in MIST-15 and BERMA MMES did not significantly covary (cov(S-c15,S-bmmes)= .138, *p*=.945). The third and final model was constructed of latent growth models of the RM latent variable, MIST 15-minute scores, and BERMA MMES, with covariances between their intercepts and slopes (Figure 20D). The model was identified, but did not did not meet appropriate thresholds (i.e., $\chi^2$=33.69, *df*=17, *p*=.009; NFI=.783; TLI=.784; CFI=.869; RMSEA=.132), suggesting that this model also did not fit the data.

***Hypothesis 6***

Finally, to address the sixth hypothesis (i.e., data would be best fit by a model of the associations between changes in fatigue, CSU, and perceived efficacy), a model was constructed of latent growth models of fatigue, CSU number, and BERMA MMES, with covariances between their intercepts and slopes (Figure 21). The model was identified and evidenced acceptable model fit indices ($\chi^2$=6.601, *df*=6, *p*=.359; NFI=.958; TLI=.990; CFI=.996; RMSEA=0.042). Furthermore, all covariances between the intercepts and slopes were significant (all *p*s<.04), supporting Model 21 as a candidate for best-fitting analysis.

***Best-Fit Analysis and Aim 2 Summary***

Across all Aim 2 models, only Model 19 and Model 21 evidenced acceptable fit indices and retained significant covariances between the slopes and the intercepts of the variables. Model 19 was more parsimonious (i.e., Model 19 AIC=17.429 vs. Model 21 AIC=36.601) and evidenced better fit indices (i.e., Model 19 RMSEA=.000 vs. Model 21 RMSEA=.042). However, Model 19 did not account for effects of fatigue on CSU number and BERMA MMES. In contrast, Model 21 revealed significant covariances between fatigue, CSU number, and BERMA MMES (all *p*s<.04), suggesting that both CSU number and BERMA MMES covary significantly with fatigue. To further investigate, the fit indices of Model 21 were compared to a nested model assuming no covariance between the intercepts and slopes of CSU number and fatigue. Compared to Model 21, the nested model revealed significantly poorer model fit indices ($\chi^2$=12.485, *df*=2, *p*<.002), indicating that inclusion of fatigue as a covariate provides a more

accurate test of the effects of CSU number on BERMA MMES. Together, these data supported selection of Model 21 as the best-fitting model for Aim 2. Unstandardized estimates and covariances for the Aim 2 final model are presented in Table 11.

## DISCUSSION

Fatigue and memory impairment are each highly prevalent in HIV disease (e.g., Heaton et al., 2011; Jong et al., 2010), and impact adherence to antiretroviral therapy. The current study explored the relationships between fatigue, memory impairment, and adherence. The first aim was to determine the best-fitting model of the relationships between fatigue, compensatory strategy use, retrospective and prospective memory impairments, and adherence. We expected that fatigue and memory would each be independently and synergistically associated with worse adherence; that strategy use would mediate the effect of memory impairments on adherence; and that fatigue would dampen the ameliorating effect of strategy use on adherence. Adherence was most parsimoniously represented by contributions from measures of perceived efficacy of medication management and objective medication-taking behavior, but not from self-reported adherence. In contrast with expectations, the data were fit best by a model reflecting direct and covarying negative effects of fatigue and strategy use on adherence, which were independent from a direct positive effect of prospective memory controlled for retrospective memory on adherence. The second aim was to determine whether changes in fatigue, CSU, and memory performance were associated with changes in perceived efficacy over a one-year period. We hypothesized that changes in fatigue, CSU, and memory would each be independently associated with changes in perceived efficacy, but the data would be fit best by a model of the associations between changes in fatigue, CSU, and perceived efficacy. While independent models of links between changes in exogenous variables and perceived efficacy evidenced either poor fit or nonsignificant relationships, consistent with expectations, the data were fit best by a model including changes in fatigue and CSU, but not memory, as significant covariates of change in perceived efficacy.

### Aim 1

In the initial aim, we explored how fatigue, memory, CSU frequency, and adherence were interrelated. Building from the Aaronson et al. (1999) model of fatigue, we hypothesized that fatigue and memory impairments would be associated with worse adherence, driven by awareness (fatigue) or evidence (performance on memory tasks) of decreased capacity for task completion due to inadequate

resources. We also expected that fatigue and memory impairments would act synergistically on adherence, such that participants with both factors would evidence significantly worse adherence than participants with either factor alone. Finally, use of compensatory strategies was expected to circumvent reliance on memory-related resources, and thus improve adherence. However, fatigue was expected to dampen the ameliorating effect of strategy use on the relationship between memory impairments and adherence.

Broadly, the best-fitting Aim 1 model only partially reflected our hypothesized model. Consistent with our original model, (1) fatigue was linked to poorer adherence; (2) the effects of fatigue on adherence was not better explained by the effects of depression on adherence; (3) PM was associated with better adherence; (4) the effects of fatigue and strategy use on adherence covaried; and (5) age and pill burden did not better explain the relationships between these variables. However, the final Aim 1 model deviated from our original model in several meaningful ways: (1) the effects of fatigue and memory were completely independent from one another; (2) RM was not directly associated with adherence; (3) strategy use did not mediate the relationship between memory and adherence; (4) strategy use was associated with worse adherence; and (5) fatigue covaried with, but did not dampen, the effects of strategy use on adherence.

***Hypothesis 1***

*Fatigue and Memory*

Our first hypothesis was that fatigue and memory impairment would affect adherence synergistically. However, best-fit analyses (i.e., the final Aim 1 model) demonstrated that the effects of fatigue and memory on adherence were completely independent from one another. Furthermore, the models that incorporated fatigue/RM and fatigue/PM interaction terms (Figure 5) evidenced very poor fit to the data despite multiple respecification attempts. In other words, no relationship was observed between awareness of diminished resources and evidence of objective deficit in memory resources, and they exhibited independent effects on adherence. This finding supports and extends the results of prior literature reporting no significant link between fatigue and neuropsychological functioning (e.g., Heaton

et al., 1995; Millikin et al., 2003). This finding also maps onto the findings of prior investigations of the links between memory and other neuropsychiatric constructs in seropositive populations. Most cross-sectional (e.g., Kalechstein et al., 1998) and longitudinal (e.g., Cystique et al., 2007) studies have not found a systematic link between depression and memory, though a few studies have reported significant relationships between verbal memory and aspects of depression (e.g., Castellon et al., 2006). Similarly, prior data failed to show robust relationships between apathy and memory (e.g., Rabkin et al., 2000; Robinson-Papp et al., 2008).

*Fatigue and Adherence*

Consistent with our hypothesized model and with the findings of prior literature (Johnson et al., 2005; Trotta et al., 2003), self-reported fatigue conferred a greater risk of suboptimal adherence. In other words, individuals who reported greater levels of fatigue were also more likely to take a lower percentage of their prescribed doses, and to perceive themselves to be less efficacious at managing medications. Follow-up analyses indicated that this relationship was driven by a negative relationship between fatigue and perceived efficacy (Figure 15), consistent with findings of Woods et al. (2008b), who reported a significant relationship between fatigue and perceived efficacy, and with the results of Woods et al. (2009a), who found no relationship between fatigue and objective medication-taking behavior.

Considering the well-established relationship between fatigue and depression in seropositive populations (e.g., Ferrando et al., 1998), and significant effects of depression on adherence (e.g., Gonzalez et al., 2011), one likely explanation for this finding is that fatigue was an indicator of underlying depressive symptomatology rather than a direct actor on adherence. To test this possibility, depression was included in the final Aim 1 model as a covariate of the effects of fatigue, CSU frequency, and memory on adherence (Figure 13). Consistent with prior findings, depression evidenced a significant negative effect on adherence. Additionally, the effects of depression on adherence covaried significantly with the effects of fatigue and RM on adherence. In other words, the effects of depression on adherence influenced, and were influenced by, the effects of fatigue and memory on adherence. However, fatigue retained a significant effect on adherence in this model, indicating that inclusion of depression in the

model did not better account for the effect of fatigue on adherence. In other words, despite significant association with depression, fatigue retained an independent effect on adherence. This finding extended prior work by Ferrando and colleagues (1998), who reported that fatigue evidenced independent contributions to disability and physical limitations despite significant associations with depression. Furthermore, inclusion of depression to the Aim 1 final model worsened the model fit, indicating that the data were fit best when depression was not included as a covariate.

Given the inclusion of fatigue as a symptom of depression in the DSM-5 (American Psychiatric Association, 2013), and prior conceptualizations of HIV-related fatigue as a symptom of depression (e.g., Millikin, Rourke, Halman, & Power, 2002), perhaps fatigue and depression so closely measured the same construct that the redundancy of including both measures in the model was responsible for the reduction in model fit. We addressed this possibility by testing whether replacement of fatigue with depression would improve the fit of the other hypothesized relationships to the data (Figure 14). Notably, replacement of fatigue with depression worsened the fit of the model considerably. In other words, depression did not better explain the effect of fatigue on adherence and the role of fatigue in the rest of the model.

These results are consistent with prior data indicating that despite high comorbidity with depression, HIV-related fatigue is a condition that is clinically distinct from depression (e.g., Breitbart et al., 1998). For example, Barroso and colleagues (2016) demonstrated that effective treatment for depression could partially improve but not fully resolve HIV-related fatigue. By underscoring the clinical distinction between depression and fatigue, these data also underscore the importance of including assessment and treatment of both fatigue and depression into routine HIV-related care. As treatment of depression has already been linked to improvements in adherence (e.g., Sin & Matteo, 2014), an important future study will be to assess whether successful treatment of fatigue would result in similar benefits to adherence.

These data also supported the conceptual distinction between fatigue and depression. As the results of best-fit analyses supported consideration of fatigue and depression as separate constructs,

fatigue is unlikely to be merely a reflection of affective distress. In the original model, fatigue was conceptualized as an awareness of diminished resources. Returning to that conceptualization of fatigue, perhaps the relationship between fatigue and adherence is driven by a perceived decrease in the resources necessary to perform adherence-related activities. However, the nature of the link between suboptimal adherence and the perception of fewer resources to allocate for adherence-related activities is relatively understudied. For example, while Siegel, Schrimshaw, and Raveis (2000) noted that some participants reported feeling "too tired" to take their medications, they did not explore what it meant for participants to be "too tired" to take their medications.

One avenue for exploring the link between fatigue and adherence would be to consider how fatigue affects daily functioning more broadly. One recent study investigated how HIV-related fatigue is perceived to interfere with daily functioning. Participants reported that fatigue most often interfered with the ability to think quickly and clearly, plan activities ahead of time, perform household chores, exercise, work, and engage in recreational activities (Harmon et al., 2009). Participants also indicated that fatigue was most impactful on motivation, concentration, and drowsiness. While broad and largely subjective, many of these concepts likely reflect relevant resources for adherence-related behaviors, particularly concepts like clear thinking, planning, motivation, and concentration. Thus, these data offer insights into potential mechanisms underlying the relationship between fatigue and adherence.

Among these concepts, motivation is one likely mechanism for the effects of fatigue on adherence. Motivation has been incorporated in various models of health behavior, including the information-motivation-behavioral skills model (IMB; e.g., Fisher et al., 2006) and self-determination theory (e.g., Williams et al., 2000), both of which have been applied specifically to cART adherence (e.g., Fisher et al., 2008; Kennedy, Goggin, & Nollen, 2004). In the IMB model, motivation to adhere is thought to be driven by favorable attitudes about cART adherence, unfavorable attitudes about nonadherence, and perceiving that others will support their adherence (e.g., Fisher et al., 2008). Along with adherence information, or the accuracy and depth of medication- and adherence-related knowledge, motivation is thought to be related to performance of behavioral skills, which incorporates both objective

performance and perceived efficacy. Finally, behavioral skills are expected to be directly associated with adherence, while the effects of information and motivation on adherence are thought to be mediated by behavioral skills. In other words, the IMB model posits that an informed and/or motivated person who lacks the objective skills necessary to complete adherence-related tasks, or does not perceive self-efficacy to do so, will have difficulty maintaining optimal cART adherence (Amico, Toro-Alfonso, & Fisher, 2005). This model has been supported by some prior data (for a review, see Fisher et al., 2008). In one study using SEM, information and motivation were found to be independently associated with self-reported behavioral skills, which in turn was independently associated with self-reported adherence. Motivation and information were not significantly associated, and neither was directly associated with self-reported adherence (Amico, Toro-Alfonso, & Fisher, 2005).

In self-determination theory (SDT), level of patient autonomy is thought to be a significant predictor of health-related behaviors (William et al., 2000). Autonomous motivation is the crux of SDT, and is described as the extent to which participants engage in specific health behaviors of their own volition, because such behaviors are important to them, rather than because of external pressures. Like the IMB model, autonomous motivation is thought to be related to autonomous support, or the perception that one's healthcare providers and family support adherence behaviors (Williams et al., 1998). Finally, the relationship between autonomous motivation and health behavior is thought to be mediated by perceived competence to execute the behavior.

Extending SDT to cART adherence, Kennedy, Goggin, and Nollen (2004) postulated that seropositive individuals are more likely to have positive attitudes about adherence if they perceived they chose freely to engage in cART because doing so was personally important, and not because of external forces. To test the fit of these SDT concepts to adherence, Kennedy, Goggin, and Nollen (2004) constructed an SEM model of the hypothesized relationships between autonomous support, autonomous motivation, perceived competence, and adherence. Psychological distress, measured by three subscales of the POMS, was also included in the model. Autonomous support significantly predicted autonomous motivation, which in turn predicted perceived competence, which then predicted self-reported adherence.

Autonomous motivation was also significantly associated with the depression/dejection scale of the POMS (*r*=-.18), though the effect of this relationship on adherence was not directly assessed in the SEM model (Kennedy, Goggin, & Nollen, 2004). It is worth noting that while fatigue was considered in the previous study design, it was included as one of 26 somatic symptoms associated with HIV infection, which likely confounded any putative effects of fatigue to the model. The POMS fatigue/inertia subscale was not included in the study.

These prior findings have interesting conceptual implications for the current study. First, both studies indicated a link between motivation and perceived efficacy. In the Amico (2005) study, motivation was significantly associated with self-reported behavioral skills, a variable that was designed to reflect both objective skill knowledge and perceived efficacy to use the skills effectively (e.g., participants responded to items like, "I have no problems taking my combination therapy medications correctly, even when it's difficult to work them into my schedule."). Similarly, Kennedy and colleagues (2004) reported a significant association between autonomous motivation and perceived competence to execute adherence-related behaviors, which was "likened" to self-efficacy. Given our inclusion of perceived efficacy in the adherence latent variable, these findings suggest that motivation could have a significant effect on adherence in the Aim 1 final model. Second, given the well-established associations between depression and fatigue, the significant relationship between depression and autonomous motivation observed by Kennedy and colleagues (2004) may reflect a similar link between fatigue and motivation.

Taken together, these data support the possibility that the effect of fatigue on adherence is at least partly related to the effects of fatigue on motivation, and of motivation on adherence. To test this theory, a future study could include adherence-related motivation as a mediator of the relationship of fatigue and adherence in the final Aim 1 model. Investigations of the effect of fatigue on motivation to adhere might be particularly relevant for individuals who conceptualize their experience of fatigue as a side effect of cART. Participants sometimes report avoidance of adverse side effects as a reason for missing cART doses (e.g., Waldrop-Valverde et al., 2006). Thus, participants who experience fatigue as a side effect of

cART may be even less motivated to maintain adherence to the medications that caused their fatigue. As the current study did not ask participants about the perceived cause of their fatigue, an important future study would be to examine whether individuals who attribute their experience of fatigue to medication side effects show a stronger effect of fatigue on adherence than those who attribute fatigue to the disease process. The findings of this future study would support new avenues for assessment and interventions of fatigue-related interference to adherence. Specifically, if fatigue has a greater impact on motivation to adhere for participants who perceive it as a cART side-effect, future treatment studies could adapt existing IMB interventions (e.g., Wagner et al., 2006) and adherence-related motivational interviewing approaches (e.g., Krummenacher et al., 2011) to address the effects of fatigue on motivation to adhere to cART.

In summary, while these data indicated that the effect of fatigue on adherence was not driven by depression, there remain myriad other factors that could be driving the effect of fatigue on adherence, including low motivation, or other adverse medication side effects (e.g., diarrhea or insomnia). Additionally, it is important to note that the current study assessed only acute fatigue; thus, the presence of chronic fatigue may differentially impact adherence and the other variables in the Aim 1 final model. Ultimately, fatigue remains a vague constitutional symptom that warrants further investigation of its complex nature, its effects on adherence, and its predictors in seropositive populations.

*Memory and Adherence*

PM also directly affected adherence in the expected direction, with better performance on long-delay PM tasks predicting better adherence. Specifically, participants who demonstrated better performance on PM tasks over 15 minute and/or 24 hour delays were also more likely to have better rates of observed adherence to cART, and/or better perceived efficacy to manage their medications. Post hoc analyses revealed that the relationship between PM and adherence was driven by a significant relationship between PM and perceived efficacy to manage medications (Figure 15). This finding is consistent with that of Woods and colleagues (2008b), who found that time-based and 24-hour delay PM were significant predictors of perceived efficacy. However, PM did not retain a significant relationship with objective

medication-taking behavior in post hoc analyses, even when perceived efficacy was removed from the model completely (Figure 15D). This finding contrasts with that of another study by Woods et al. (2009a), who reported that PM significantly predicted medication-taking behaviors. However, the earlier finding reflected a relationship between medication-taking behavior and loss-of-time errors on the MIST, indicating that deficits in time-based PM specifically were linked to medication-taking behavior. In contrast, long-delay PM in the current study reflected both time-based and event-based PM performance. Together, these data suggest that time-based PM is more predictive of medication-taking behavior than summary PM performance (i.e., both time-based and event-based) over longer delays, though both elements of PM are strongly associated with perceived medication management efficacy.

Additionally, the relationship between PM and adherence appeared to be driven primarily by the 15-minute PM delay scores, but overall the data were fit best by inclusion of both delay intervals in the model (Figure 16). The link between adherence and PM performance after a 15-minute delay is consistent with the findings of Poquette and colleagues (2013), who observed that participant performance on the 15-minute, but not the 2-minute, PM subscale was associated with worse adherence. The current findings also extend the literature by considering the effects of both the 15-minute delay and a longer delay interval (i.e., 24 hours) on the relationship between PM performance and adherence. While the 24-hour PM delay scores entered alone in the final model resulted in poor model fit, inclusion of the 24-hour PM delay scores in the PM latent variable with the 15-minute PM delay scores produced a model with significantly better fit indices than the model with the 15-minute PM delay scores alone. In other words, while PM performance after a 15-minute delay was significantly related to adherence, inclusion of PM performance after a 24-hour delay significantly improved the fit of the relationship between PM and adherence. Together, these data support the utility of 15-minute PM delay performance for predicting adherence, but also suggest that a more complete understanding of the relationship between PM and adherence requires inclusion of PM performance over longer, and thus more naturalistic, delays.

It is somewhat surprising that inclusion of the 24-hour PM delay scores alone substantially worsened the fit of the model, despite prior evidence of associations between 24-hour PM delay

performance and perceived efficacy (Woods et al., 2008b), and given that naturalistic PM tasks, particularly those related to adherence, can require delay intervals of days or weeks. Examples include remembering to attend scheduled appointments, to call providers during business hours, and to refill prescriptions on time. Thus, one might have expected 24-hour PM delay performance to fit the model as well, or perhaps better than, the shorter PM delay performance. However, it is worth noting that unlike the 15-minute PM delay scores, which were comprised of PM performances across four different tasks, the 24-hour PM delay scores only reflected performance on one naturalistic task. As performance on one naturalistic 24-hour task does not reflect how participants might perform on average across multiple long-delay naturalistic tasks, one future study could be to re-apply the model to data that include a measure of 24-hour or longer PM delay performance that comprises multiple trials or multiple tasks. Such a study would determine whether the 15-minute PM delay performance retains the relatively stronger relationship with adherence when compared with a more comprehensive measure of 24-hour PM delay performance. Results from this study would provide more information regarding the utility of 15-minute PM delay scores for predicting adherence.

Unexpectedly, the best-fitting model did not include a direct effect of RM on adherence. Notably, iterative model generation and respecification produced a model reflecting a significant direct effect of RM on adherence, but only in the absence of a direct effect of PM on adherence (Figure 3G). While this alternative model evidenced good model fit indices and was consistent with prior literature supporting a link between adherence and RM performance (e.g., Ettenhofer et al., 2010; Hinkin et al., 2004), the fit of the model to the data was noticeably weaker than that of the Aim 1 final model. Curiously, none of the models evidenced a significant effect of either RM or PM on adherence when both direct effects were included in the model. However, the results of best-fitting model analyses supported the inclusion of RM as a covariate of the effect of PM on adherence. Specifically, the fit of the model to the data worsened significantly when RM was removed from the model entirely (Figure 3H).

Together, these findings are consistent with the theoretical position that RM is a necessary but not sufficient resource for successful PM performance (Gupta et al., 2010; Woods et al., 2006; Woods et al.,

2008a) including adherence (Woods et al., 2009a). First, inclusion of a direct effect of PM, but not RM, on adherence in the best-fitting model indicates that some aspect of PM was more directly related to adherence than RM. Second, the improved fit of the model when RM was included as a covariate of PM suggests that the availability of RM resources significantly affected the relationship between PM and adherence. This finding supports prior data that intact RM resources are necessary for successful execution of PM tasks (e.g., Carey et al., 2006). Specifically, RM resources are important for retention of the cue-intention pairing during distractor tasks, and retrieval of the intention upon detection of the cue. Without intact RM, PM is likely to fail at multiple stages, including failure to retain the cue or intention during the distractor task, or failure to retrieve the intention upon cue detection. However, the status of these RM resources does not account for the relationship between PM and adherence. One possible explanation is the difference in the circumstances of retrieval between RM and PM tasks. On RM tasks, the experimenter directs participants when to retrieve recently stored information, thus putting them into a retrieval mode (Einstein et al., 2005). By contrast, PM tasks require participants to remember to put themselves into a retrieval mode when they encounter the cue at some point in the future. Thus, the availability of RM resources becomes moot if participants fail to remember to put themselves into retrieval mode upon detection of the cue.

These conceptual differences between RM and PM have particular relevance for adherence. Intuitively, adherence is a composite of successes or failures to execute daily medication-related PM tasks, like remembering to take medications on time, or to fill prescriptions before running out. Most seropositive adults must complete these tasks at least some of the time on their own, without relying on reminders from family or friends to take their medications on time. In other words, they must retrieve their intention to take their medications or refill their prescriptions on time without relying on an external director to put them into retrieval mode. However, they require intact RM resources as well, as the ability to put themselves into retrieval mode is moot if the information to be retrieved was not retained.

Clinically, these data underscore the importance of assessing PM when addressing referral questions related to adherence. However, these data also underscore the importance of assessing RM, as

assessment of PM alone may not be sufficient to understand the full contribution of impaired episodic memory on suboptimal adherence.

***Hypothesis 2***

*Memory and Strategy Use*

Notably, the final Aim 1 model was also largely inconsistent with our second hypothesis. We predicted that compensatory strategy use (CSU) frequency would mediate the relationship between memory and adherence, such that worse memory performance would predict more frequent CSU, which in turn would be associated with better adherence than worse memory performance directly. In other words, among participants with fewer memory resources, those who used adherence-related strategies more frequently were expected to show better adherence than those who used strategies less frequently. In contrast with these expectations, RM and PM were not significantly associated with CSU frequency in the final model. Furthermore, models incorporating a mediating effect of CSU on the relationships between RM, PM, and adherence evidenced very poor fit to the data (Figure 9). Together, these findings revealed no significant relationship between memory resources and frequency of strategy use.

One possible explanation for this discrepancy is that CSU and PM were only related among older adults. Age has significant links with frequency of strategy use (Blackstone et al., 2013), memory, particularly PM (Weber et al., 2011), and adherence (Barclay et al., 2007). Older adults tend to show impairments in laboratory-based measures of PM, but successfully manage PM tasks in daily life; for example, they tend to be more adherent than younger adults. Strategy use is thought to account for this paradox. Specifically, frequency of strategy use increases as participants age, and older adults tend to use strategies more effectively than younger adults to manage PM tasks in their daily lives (Weber et al., 2011). Taken together, younger adults are less likely to use strategies regardless of PM, while older adults are more likely to show greater CSU and worse PM. Thus, controlling for age in the model could reveal a relationship between CSU and PM among older adults, which was dampened in the final model by the tendency of younger adults not to use strategies.

To test this possibility, we included age as a covariate in the final model (Figure 13G). Consistent with expectations and with the prior studies, older age was significantly associated with more frequent strategy use and worse PM. However, controlling for age in the model did not reveal the expected relationship between PM and CSU. One explanation is the relatively low proportion of older adults in the current sample. In the prior studies, participants were dichotomized into groups of younger and older adults, with mean ages ranging from 32 for the younger adults to 56 for the older adults (Weber et al., 2011). In contrast, the current study was comprised of adults between those ranges (mean age=49), and participant ages were normally distributed, indicating inclusion of a relatively small proportion of older adults compared to the prior studies. Thus, controlling for age was not sufficient to reveal a relationship between CSU and PM expected to be present only for a small percentage of the sample. Another explanation for these data is that CSU and PM are not directly related. Rather, they are indirectly associated though age, such that patterns of CSU and PM tend to change throughout the lifespan, but are not related at any one stage of life. Future studies exploring the relationships between CSU, PM, and adherence in samples of older adults are necessary to further investigate these possibilities.

Another explanation for the discrepancy between memory and CSU frequency is a difference in the role of awareness for memory and CSU. Decisions about employment of compensatory strategies are predicated on *awareness* of available resources. Specifically, participants are unlikely to use compensatory strategies if they are not aware of a deficiency in resources for which they need to compensate. Thus, the discrepancy between subjective assessment of strategy use and objective memory performance observed in the current study could reflect a lack of awareness of objective memory deficits.

This explanation is partially supported by prior data demonstrating that perceptions of available RM and PM resources are often discrepant from objective evidence of memory resource availability among seropositive populations. In one study, up to 50 percent of the seropositive cohort (N=46) showed a discrepancy between perceived and objective memory resources, and participants who denied cognitive impairments also performed worse on memory measures (Hinkin et al., 1996). Another study compared self-reported complaints of PM and RM in daily life with objective neuropsychological performance

among 75 seropositive individuals and 60 seronegative controls (Woods et al., 2007). Seropositive participants endorsed more frequent PM complaints compared to seronegatives, particularly on items related to self-initiated cue detection and retrieval. On objective neuropsychological testing, the seropositive group evidenced significantly worse PM and RM performance than the seronegative group; however, objective performance on memory measures was not related to PM complaints in either group.

However, to our knowledge, no study to date has directly assessed the relationship between memory complaints and frequency of strategy use in HIV-positive populations. Thus, one future study would be to generate alternative models that either add subjective memory complaints to the final model, or replace objective memory performance with subjective memory complaints altogether. RM and PM complaints could be assessed by the Prospective and Retrospective Memory Questionnaire (PRMQ; Smith et al., 2000), a self-report inventory that measures the frequency at which perceived memory difficulties occur in daily life. These alternative models would be tested for significant relationships between memory complaints and CSU frequency, as well as for relative fit of these models to the Aim 1 final model. These future analyses would provide further characterization of the relationships between CSU frequency, objective memory performance, and subjective memory complaints, and extend the literature by directly assessing the relationship between strategy use and memory complaints among seropositive individuals.

*Strategy Use and Adherence*

Another unexpected finding was the nature of the link between CSU frequency and adherence in the final model. We expected that more frequent strategy use would bolster adherence, consistent with prior data demonstrating that use of external strategies, especially pill box organizers, were associated with better adherence (e.g., Kalichman et al., 2005; Petersen et al., 2007). Instead, greater CSU frequency was associated with worse adherence in the final model. Follow-up analyses revealed that this link was driven by a significant negative relationship between CSU frequency and perceived efficacy to manage medications (Figure 15B), and that CSU frequency was not significantly associated with objective medication-taking behavior. In other words, individuals who reported more frequent use of strategies to

support adherence were also more likely to report less efficacy regarding medication management, but were not more likely to show better medication-taking behaviors than individuals who reported less frequent strategy use.

While surprising in the context of the expected model, these findings are partially consistent with prior data. First, the nonsignificant relationship between CSU frequency and objective medication-taking behavior dovetails with prior findings from Woods and colleagues (2009a), who observed no significant difference in PMMQ total strategy use between seropositive individuals characterized as either adherent or non-adherent based on their MEMS scores. In contrast, Blackstone and colleagues (2013) reported that greater total frequency of strategy use was associated with worse objective medication-taking behavior. Second, the significant negative association between strategy use and perceived efficacy is consistent with prior data from Woods et al. (2008b), who found that greater total frequency of strategy use, also measured by the PMMQ, was associated with lower perceived efficacy to manage medications.

The discrepancy between the current findings and those of Blackstone et al. (2013) warrants further consideration. One major difference between the current and prior studies is that the prior study did not consider the effect of perceived efficacy on the relationship between CSU frequency and objective medication-taking behavior. Integration of both findings suggests that greater CSU frequency may be significantly related to poorer medication-taking behavior, as observed in the Blackstone et al. (2013) study, but only when the relationship between greater CSU frequency and perceived efficacy to manage medications is not considered, as suggested by the current study. To test this hypothesis, we reanalyzed the Aim 1 final model with inclusion of medication-taking behavior but not perceived efficacy as the endogenous variable (Figure 13D). Consistent with expectations, removal of perceived efficacy from the model revealed a significant relationship between greater CSU frequency and worse medication-taking behavior, consistent with the findings of the Blackstone et al. (2013). Thus, the current data extend the literature by comparing the relative relationships between CSU frequency, perceived efficacy, and objective medication-taking behavior, and by demonstrating that strategy use is much more strongly related to perceived efficacy than to medication-taking behavior.

Furthermore, these data have important conceptual implications. The first implication is the nature of the link between strategy use and perceived efficacy. Individuals who reported more frequent strategy use to support adherence were also more likely to perceive themselves as less effective at managing medications. The role of awareness may also underlie these observed relationships. Participants are more likely to use compensatory strategies if they are aware of a resource deficiency for which they need to compensate. In turn, perception of reduced efficacy to manage medications may reflect perception of a resource deficiency. Thus, participants become aware of a resource deficiency, which prompts perception of themselves as less effective and increases the likelihood they will use more strategies more frequently to compensate for their perceived lack of efficacy to manage their medications.

Additionally, while individuals who reported more frequent strategy use to support adherence were also more likely to show poorer medication-taking behavior, this relationship disappeared when their level of perceived efficacy was included in the model, suggesting that CSU frequency was more strongly related to perceived efficacy than to medication-taking behavior. In other words, individuals who reported more frequent strategy use were more likely to perceive themselves as less effective at managing medications than to show worse medication-taking behavior. This discrepancy may also reflect the differing roles of awareness inherent in assessments of perceived efficacy and objective medication-taking behavior. Specifically, while participants self-assessed their CSU frequency and perceived efficacy, which by nature measured their awareness of these behaviors/perceptions, medication-taking behavior was assessed objectively using the MEMS. Additionally, self-reported adherence (i.e., ACTG) was much higher in the current study than adherence reflected by the MEMS (Table 3), indicating a discrepancy between participants' perceived adherence and their actual medication-taking behavior. These data are consistent with prior findings that self-report measures tend to overestimate adherence (e.g., Arnsten et al., 2001), and support the hypothesis that CSU frequency is more strongly linked to perceived efficacy than to medication-taking behavior because participants are more aware of their strategy use and perceived efficacy than of their medication-taking behaviors.

A final consideration of these data is the nature of the relationship between CSU frequency and medication-taking behavior when perceived efficacy was removed in the model. We had expected that increased use of strategies would be associated with better adherence, as individuals would be investing more resources into adherence-related behaviors. Instead, participants who reported more frequent use of strategies were also more likely to show worse medication-taking behaviors. One possibility is that greater frequency of strategy use reflects maladaptive use of strategies. For example, while sparse, the strongest support for strategy use as beneficial for adherence comes from pill box organizer studies (e.g., Kalichman et al., 2005; Petersen et al., 2007), which indicate that consistent use of pill boxes to organize medications is associated with better adherence. In other words, these data indicate that consistent use of one strategy improves adherence. Recall that in the current study, CSU frequency was measured by the PMMQ, a self-report questionnaire comprised of 28 strategies, half of which are internal, or cognitively-based strategies, and half are external, or behaviorally-based strategies. Participants are instructed to rate the frequency at which they use each strategy from 0 (never) to 4 (always). Total frequency scores range from 0 to 112, with higher scores reflecting both number of strategies and the frequency to which each strategy is used. Thus, participants who relied most consistently on one or two strategies to manage medications would produce relatively low scores on the PMMQ, even if they rated those strategies at the frequency level of "always." In contrast, participants who used multiple strategies less consistently would produce much higher PMMQ scores, but this pattern of strategy use may be less effective for supporting adherence. Further investigation of strategy use patterns is warranted to better understand the link between strategy use and adherence, and to determine when to intervene to improve participant strategy utilization.

*Fatigue and Strategy Use*

The last expectation of the second hypothesis was that fatigue would disrupt the mediating effect of CSU frequency on the relationship between memory and adherence. As CSU frequency did not mediate the relationship between memory and adherence, best fit analyses were used to explore the nature of the relationship between CSU frequency and fatigue. The final Aim 1 model revealed a significant

covarying relationship between the direct effects of fatigue and CSU frequency on adherence. In contrast, models incorporating an interactive effect of fatigue and CSU frequency on adherence evidenced no significant effect of the interaction terms on adherence (Figure 10). Additionally, while models reflecting mediating relationships between fatigue and CSU frequency on adherence retained significant estimates for all hypothesized paths (Figure 12), the fit of the mediation models was identical to the fit of the direct model. As the model fit was not improved by the mediation models, the cross-sectional nature of the data precluded formation of conclusions about causation, meaning that the current models could not be used to determine whether fatigue or CSU frequency mediated the other factor's relationship with adherence, or whether the two factors covaried in their effects on adherence. Thus, the direct model reflecting a covarying relationship between fatigue and CSU frequency was selected as the Aim 1 final model.

The significant relationship between the effects of fatigue and CSU frequency on adherence was positive, suggesting that participants who reported greater awareness of diminished resources were also more likely to employ a greater number of strategies, and use them more frequently, with the goal of supporting adherence. One possible explanation for this relationship is that awareness of diminished resources to adhere to medications prompts individuals to employ more strategies, and to employ them more frequently, with the aim of compensating through multiple avenues for the perceived lack of resources. An alternative explanation is that awareness of diminished resources prompts individuals to switch strategies more frequently due to a perceived lack of resources to utilize their more commonly employed strategies. One example might be failure to organize medications into a pill box due to a perceived lack of the cognitive resources necessary to perform the strategically-demanding task, instead relying on internally-based retrieval strategies to monitor whether they have taken their medications correctly, a strategy they perceive to be less cognitively demanding. A third possibility is that more frequent use of multiple strategies requires greater allocation of resources toward strategy implementation and prompting awareness of fewer resources available for other tasks, which could be experienced as increased fatigue. Ultimately, conclusions about the causality of the relationship between fatigue and CSU are precluded by the cross-sectional nature of the data.

An interesting future study would be to develop a self-report questionnaire that assesses participant reactions to the experience of fatigue in the context of strategy use and adherence. Like the PMMQ, the questionnaire would ask participants to rate the frequency at which they use different types adherence-related strategies. Then, participants could be asked to rate the strategies again based additional questions assessing possible effects of fatigue on strategy use, and assessing possible effects of strategy use on fatigue. Example questions include: (1) how likely are you to use each strategy when you are feeling fatigued? and (2) How often does using this strategy make you feel fatigued? Responses to this questionnaire could be used to determine whether individuals consciously change their use of strategies in response to fatigue, or whether the relationship between fatigue and strategy use occur outside of participant awareness. It would then be interesting to compare participant responses on this questionnaire to longitudinal data monitoring fatigue, strategy use, and adherence over time to better understand how fatigue and CSU affect each other and adherence.

***Comparison of the Original and Final Models***

In the original model, we expected that fatigue and memory impairment were synergistically associated with worse adherence, and that strategy use would account for this effect. Specifically, impaired memory was expected to be associated with worse adherence, but participants with memory impairments were expected to respond to their diminished memory resources by using adherence-related strategies more frequently, thus partially compensating for the effect of their memory impairments on adherence. Fatigue was thought to interfere with typical strategy employment, and thus further reduce adherence for participants with impaired memory. Conceptually, awareness of diminished general resources was expected to elicit perceptions that the resources necessary for strategy employment were not available, thus resulting in decreased strategy use and worse adherence. In contrast, participants with intact memory were expected to rely less heavily on strategy use to maintain adherence. Thus, in the presence of fatigue, participants with intact memory were thought to show some reduced adherence, but not to the degree evidenced by participants with impaired memory.

Notably, few of these expectations were upheld by the final model. While fatigue and memory evidenced the expected relationships with adherence, the effects of fatigue and memory on adherence were not related. The role of strategy use in the final model was also completely unexpected; rather than ameliorating the relationship between memory impairments and adherence, CSU frequency was unrelated to memory, and was negatively related to adherence. Finally, the effects of fatigue and strategy use on adherence were positively related, such that fatigue was associated with greater, rather than reduced, CSU frequency, and both were associated with worse adherence.

Awareness emerged as a unifying explanation for many of the discrepancies between the original, expected model and the Aim 1 final model. Intuitively, the decision to use compensatory strategies is predicated on awareness of a resource deficiency for which to compensate. Thus, awareness of diminished resources would be expected to be positively related to frequency of strategy use, which was observed in the Aim 1 final model. Additionally, perceptions of reduced efficacy to manage medications could be expected to reflect perceived deficiency in resources. Thus, lower perceived efficacy would be associated with awareness of diminished resources and more frequent strategy use, which was also observed in the Aim 1 final model. Given prior evidence of discrepancies between perceived memory resources and objective memory performance (Woods et al., 2007), it follows that objective memory performance would not be related to strategy use, which was observed in the final Aim 1 model. Finally, given prior evidence of discrepancies between perceived level of adherence and objective medication-taking behavior (Arnsten et al., 2001), awareness of diminished resources and strategy use would not be expected to affect medication-taking behavior, which was also reflected in the final model.

Support for the underlying role of awareness in many of these observed relationships is reflected in a recent study in our lab exploring the associations between pill burden, PM, CSU, and perceived efficacy. Sheppard and colleagues (2016) observed that better time-based PM was related to better adherence for younger adults (<50) with low pill burden (ARV and non-ARV, <7), but not for younger adults with high pill burden. Post hoc analyses of possible explanatory factors revealed that younger participants with high pill burden reported higher CSU frequency and significantly lower ratings of

perceived efficacy to manage medications than younger individuals with low pill burden. Sheppard and colleagues (2016) opined that the relationship between time-based PM and adherence in the low pill burden group could be explained by underutilization of compensatory strategies by these younger adults, which could have buffered the effects of impaired time-based PM on adherence.

In this study, high pill burden appeared to contribute to perceptions of a resource deficiency. In turn, younger adults with high pill burden perceived themselves as less effective at managing medications, and were likely to use strategies more frequently to compensate for the perceived lack of efficacy. In contrast, younger adults with low pill burden perceived themselves to be more effective at managing medications and were less likely to use adherence-related strategies. However, this latter group was also more susceptible to effects of time-based PM performance on medication-taking behavior. Together, these findings indicate two different levels of strategy use employment. First, awareness of a resource deficiency (i.e., high pill burden), reflected by lower perceived efficacy, resulted in more frequent strategy use. In contrast, lack of awareness of a resource deficiency (i.e., lower time-based PM), was not associated with lower perceived efficacy and did not affect frequent strategy use, but did impact medication-taking behavior.

Given the significant relationships between pill burden, CSU frequency, PM, and perceived efficacy observed in the prior study, and some of the parallel findings between the prior and current studies, post hoc analyses were conducted to determine whether pill burden was a significant covariate of the final Aim 1 model. Best-fit analyses revealed that pill burden did not significantly affect adherence when included in the Aim 1 final model, indicating that pill burden did not better explain the effects of fatigue, CSU, and memory on adherence (Figure 13H). However, pill burden covaried significantly with CSU frequency and PM, consistent with the prior study. Specifically, higher pill burden was associated with greater CSU frequency, thus providing additional support that higher pill burden may prompt participants to perceive a resource deficiency. Higher pill burden also covaried with PM, such that higher pill burden was associated with worse PM. This finding was initially surprising, given the results of the prior study that PM was more strongly related to adherence at lower pill burden (Sheppard et al., 2016).

However, as pill burden includes both ART and non-ART burden, it is an indicator of participants' general health as well as their HIV-related health. Thus, higher pill burden may also reflect greater incidence of other common chronic health conditions (e.g., diabetes, hypertension, and hyperlipidemia), many of which are associated with white matter disease, and many of which may independently contribute to impairments in prospective memory (e.g., obesity; Gunstad et al., 2010).

Interestingly, pill burden was also related to fatigue, such that participants with higher pill burden also reported greater levels of fatigue. This finding may reflect fatigue as a medication side effect, such that more complex medication regimens are more likely to cause side effects like fatigue. Alternately, participants with higher pill burden may report greater levels of fatigue because they expect to feel more fatigued, because of their high pill burden. One reason is that if participants conceptualize fatigue as a side effect of medications, they may be more sensitive to experiencing fatigue and thus more likely to report fatigue at higher levels. Another, not necessarily mutually exclusive, possibility is that fatigue and pill burden both contribute to perceptions of resource deficiency. For example, in the context of awareness of diminished resources, higher pill burden contributes to the perception of further resource diminishment.

However, the awareness discrepancy explanation does not address prior data reporting links between strategy use and better performance on PM tasks in both seropositive (Weber et a., 2011) and seronegative (Aronov et al., 2015) samples of older adults, which support the original model hypothesis that increased strategy use would be associated with better adherence. Furthermore, this explanation does not intuitively account for the significant relationship between PM and perceived efficacy revealed by post hoc analyses (Figure 15B), and reflected by prior data (e.g., Woods et al., 2008b). Specifically, if perceived efficacy is thought to be associated with awareness of a resource deficiency, and seropositive adults often evidence discrepancies between their perceived and actual level of PM resources (Woods et al., 2007), it is less clear why PM is significantly related to perceived efficacy.

Consideration of aging effects on PM resource awareness may account for both these divergent observations, and for the discrepancies between the original model and the final model. Prior data in

seronegative samples suggest that accurate awareness of PM resources increases over the lifespan. One study observed that older adults more accurately predicted their performance on a naturalistic PM task compared to younger adults (Schnitzpahn et al., 2011). Another study found that self-reported PM was significantly related to objective PM performance among older adults who reporting fewer PM complaints (Zeintl et al., 2006). More accurate awareness of PM resources among older adults has been hypothesized to underlie the higher effectiveness of strategy employment by older adults in daily life compared to younger adults, as noted by prior data (Weber et al., 2011). Specifically, Kliegel and colleagues (2008b) argued that due to greater experience with naturalistic PM tasks, older adults evaluate their PM performance more accurately, and thus select and employ strategies more effectively to achieve optimal results. Together, these data suggest that at least some of the hypotheses of the original model, particularly the expected relationships between PM, strategy use, and adherence, are more consistent with patterns of performance observed in older, rather than younger adults, and may be upheld in samples of older adults.

Returning to the Aim 1 final model, the lifespan view of PM resource awareness may also explain the link between PM and perceived efficacy. While participants in their middle years may not be as aware of their PM resources as older adults, nor as acutely aware of their PM resources in the moment as they are of other factors like fatigue or strategy use, they may possess rough estimates of their typical PM resources from repeated exposure to their performances on PM tasks over time. Given the role of PM for adherence, it follows that rough estimates of PM resources would be incorporated into self-assessments of efficacy to manage medications, thus producing the observed associations between PM and perceived efficacy. In contrast, rough estimates of PM resources would not be informative enough to influence moment-to-moment decisions about strategy employment, thus producing the non-significant relationship between strategy use and memory observed in the final model. Finally, lack of consideration of PM resources in decisions about strategy employment may contribute to the observed link between strategy use and lower perceived efficacy. Together, this conceptualization suggests dynamic relationships between fatigue, CSU, memory, and perceived efficacy, wherein evaluation of medication management

efficacy involves ongoing assessments of resource availability related to estimates of PM and current levels of fatigue and compensatory strategy deployment.

***Summary***

In summary, findings from the first aim indicated that fatigue and CSU frequency were associated with each other and with worse adherence, while better PM, controlled for RM, was independently associated with better adherence. These relationships were driven by associations with perceived efficacy to manage medications, such that higher fatigue, greater CSU frequency, and worse PM were all associated with lower perceived efficacy. Depression did not better explain the effects of fatigue in the final model, and motivation was proposed as a putative link between fatigue and adherence. In contrast with expectations of the original model, CSU was not related to memory, and fatigue was associated with increased rather than decreased CSU frequency. Age and discrepant levels of awareness between perceived and objective resource deficits were proposed as likely explanations for the lack of agreement between the original model and the final aim 1 model.

**Aim 2**

The second aim of the current study was to investigate whether changes in fatigue, strategy use, and memory impairment were associated with changes in perceived medication management efficacy over a one-year period. We hypothesized that changes in fatigue, CSU, and PM (controlled by RM) would each be independently associated with changes in perceived efficacy over the one-year period. Specifically, increases in fatigue and CSU were expected to be associated with lower perceived efficacy, while better PM would be associated with higher perceived efficacy. Finally, given the strong interrelationships between fatigue, CSU, and perceived efficacy in the aim 1 final model, we hypothesized that the aim 2 data would be best fit by a model incorporating the relationships between changes in fatigue, CSU, and perceived efficacy over time. We addressed these hypotheses by constructing latent variables of fatigue, PM, CSU, and perceived efficacy at baseline, and latent variables of change in each factor over one year, and then testing the associations between the baseline latent variables and between the change latent variables. Of note, we used CSU number instead of frequency to

investigate whether changes in the number of strategies used (rather than both the change in CSU number and frequency) were associated with the changes in perceived efficacy. The CSU number was calculated by dividing the number of strategies used by the total number of strategies. This methodological adjustment permitted us to address our aim 1 conceptualization that number, rather than frequency, of strategies may underlie the negative relationship between CSU frequency and perceived efficacy.

Latent growth modeling revealed partial support of these hypotheses. First, independent models of perceived efficacy and fatigue or CSU evidenced the expected relationships between changes in perceived efficacy and changes in fatigue or CSU number over time. However, the model of fatigue and perceived efficacy showed poor model fit, indicating that these hypothesized relationships did not sufficiently reflect the data (Figure 18). Additionally, while the best-fitting model of PM and perceived efficacy evidenced good model fit (Figure 20C), the model did not reveal a significant relationship between changes in PM and perceived efficacy. Finally, the data were fit best by a model including changes in fatigue, CSU, and perceived efficacy, as expected by our final hypothesis.

While a significant association between changes in fatigue and perceived efficacy was revealed by the independent model as expected, the model evidenced poor fit indices. Thus, despite indicating that changes in fatigue and perceived efficacy covary significantly across time, the finding also suggests that the link between fatigue and perceived efficacy was not sufficient for capturing the underlying patterns in the data. In contrast, the latent growth model reflecting independent associations between CSU number and perceived efficacy evidenced excellent model fit (Figure 19). Furthermore, consistent with expectations, the model revealed significant relationship between changes in CSU number and perceived efficacy, such that increases in CSU number were significantly associated with decreases in perceived efficacy. In other words, participants who reported increasing the number of adherence-related strategies they used were also more likely to report decreases in perceived efficacy.

The best-fitting latent growth model reflecting independent associations between PM and perceived efficacy also evidenced excellent model fit (Figure 20C). This model was constructed of associations between 15-minute PM delay and perceived efficacy at baseline and in changes over time.

RM was not included, as inclusion of RM resulted in significantly worse fit of the model to the data (e.g., Figure 20D), further underscoring the relatively stronger role of PM than RM for perceived efficacy observed by prior data (e.g., Woods et al., 2008b). However, in contrast with our hypothesis, changes in 15-minute PM delay were not significantly associated with changes in perceived efficacy.

Finally, results of best-fit analysis supported our last hypothesis that the data would be best fit by a model incorporating CSU number, fatigue, and perceived efficacy. The incorporated model showed significantly improved fit of the model to the data compared to that of the independent model of fatigue and perceived efficacy (Figure 21). Consistent with the independent aim 2 models, the incorporated model revealed significant negative relationships between change in perceived efficacy and change in CSU number, and between change in perceived efficacy and change in fatigue. Finally, the model revealed a significant relationship between changes in fatigue and CSU number, such that increases in fatigue over time were accompanied by increases in CSU number. Moreover, post hoc comparison of nested models revealed that assumptions of nonsignificant relationships between fatigue and CSU number produced a model with significantly worse fit to the data, providing further evidence that the data were not best reflected by independent models of fatigue or CSU number with perceived efficacy. Together, these findings indicated selection of the model incorporating fatigue, CSU number, and perceived efficacy as the best-fitting aim 2 model, thus supporting our final hypothesis.

Another important finding was that across the aim 2 models, the relationships at baseline between CSU, fatigue, and perceived efficacy, and between PM, RM, and perceived efficacy, mirrored those of the aim 1 final model. While unsurprising given the overlapping sample data between aim 1 and aim 2 at baseline, this finding indicates that the relationships observed in aim 1 were robust enough to retain significance in the smaller aim 2 sample. This finding is more notable with regard to CSU number. Specifically, the significant negative relationship between CSU number and perceived efficacy at baseline supports our hypothesis that CSU number is a significant element of the relationship between CSU frequency and perceived efficacy observed in the Aim 1 final model. While not conclusive, this finding also supports our conceptualization that the number, rather than frequency, of strategies may drive the

negative relationship between CSU frequency and perceived efficacy observed in aim 1. However, future analyses comparing the effects of different patterns of strategy use (e.g., more strategies more frequently, more strategies less frequently, fewer strategies more frequently, or fewer strategies less frequently) on perceived efficacy are warranted to better understand these relationships.

***Summary***

Taken together, the aim 2 findings indicate that greater fatigue and CSU number are associated with lower perceived efficacy at baseline; that increases in fatigue over time are associated with increases in CSU number; and both of which are associated with decreases in perceived efficacy. In contrast, better PM performance at 15-minute delays is associated with better perceived efficacy at baseline, but changes in PM are not significantly related to changes in perceived efficacy over time. While a few prior studies have employed longitudinal designs to investigate changes in fatigue (e.g., Barroso et al., 2015) or memory over time (e.g., Sheppard et al., 2015) in seropositive individuals, the majority of prior studies of the relationships between memory, fatigue, strategy use, and perceived efficacy in HIV disease have used cross-sectional designs. Consequently, these data are among the first to investigate changes in the relationships between these factors over time.

These data also provide additional support for the conceptualization that discrepancies in level of awareness of fatigue and strategy use compared to awareness of PM resources contributes to the independent effects of these variables on perceived efficacy. Specifically, the best-fitting model revealed that fatigue, CSU number, and perceived efficacy all covary at baseline and across time points, reflecting the dynamic interplay between these factors hypothesized during interpretation of aim 1 results. In contrast, despite the significant link between PM and perceived efficacy at baseline, changes in PM were not associated with changes in perceived efficacy over time, suggesting a relative lack of sensitivity of perceived efficacy to changes in PM resources over time, which in turn is indicative of reduced awareness of changes in PM resources compared to changes in fatigue and strategy employment over time.

**Summary and Conclusions**

The current study revealed dynamic relationships between fatigue, strategy use, memory, and adherence across both cross-sectional and longitudinal designs. At baseline, greater fatigue and strategy employment were associated with each other and with lower adherence, while better PM (controlled by RM) was associated with better adherence; and each of these relationships was driven by perceived efficacy to manage medications. Covariate analyses revealed that these interrelationships were not better explained by the effects of age, depression, or pill burden on adherence or on the other factors. Longitudinal analyses demonstrated that the baseline interrelationships between fatigue, strategy use, and perceived efficacy were replicated over time, such that increases in fatigue and strategy use over time were associated with one another and with decreases in perceived efficacy. In contrast, changes in PM were not associated with changes in perceived efficacy. Awareness discrepancies between perceived and objective resource deficits were proposed as a likely explanation for the strength of the relationship between fatigue and strategy use, and for the nonsignificant relationship between PM and strategy use. Additionally, age and age-related changes in awareness discrepancies were proposed as likely explanations for the lack of agreement between the original model and the final aim 1 model.

Clinically, these data underscore the importance of assessing RM, PM, and fatigue as part of routine HIV-related care, particularly in cases of suspected nonadherence. Further investigations will be necessary to determine the utility of these interrelationships for predicting later nonadherence, which could inform cART regimen prescribing decisions to address nonadherence early in treatment. With regard to generalizability of the current findings, ongoing changes in cART regimen recommendations will necessitate follow-up studies with participants taking the newer regimens. For example, while only a few participants in the current study were taking an integrase strand transfer inhibitor (INSTI; N=6), INSTIs are now included in recommended cART regimens for most cART-naïve patients (DHHS, 2016). Future studies of participants on INSTIs are particularly important, as insomnia is a common adverse side effect of these medications. Additionally, the current study sample consisted primarily of well-educated

Caucasian men from an urban setting, so the external validity of these observed relationships in the greater national and international settings remains to be assessed.

Finally, future research is warranted in other areas as well, including: (1) the relationship between fatigue and motivation in adherence, and the effects of conceptualizing fatigue as a medication side-effect on adherence; and (2) the roles of age and accurate awareness of PM resources on the relationships between fatigue, PM, strategy use, perceived efficacy, and medication-taking behavior in seropositive populations.

## REFERENCES


Aaronson, L. S., Teel, C. S., Cassmeyer, V., Neuberger, G. B., Pallikkathayil, L., Pierce, J., ... & Wingate, A. (1999). Defining and measuring fatigue. *Image: Journal of Nursing Scholarship, 31,* 45-50.

Albert, S. M., Weber, C. M., Todak, G., Polanco, C., Clouse, R., McElhiney, M., ... & Marder, K. (1999). An observed performance test of medication management ability in HIV: relation to neuropsychological status and medication adherence outcomes. *AIDS and Behavior, 3*, 121-128.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th Ed.). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (DSM-5). Washington, DC: American Psychiatric Association.

Amico, K. R., Toro-Alfonso, J., & Fisher, J. D. (2005). An empirical test of the information, motivation and behavioral skills model of antiretroviral therapy adherence. *AIDS Care, 17,* 661-673.

Ammassari, A., Murri, R., Pezzotti, P., Trotta, M. P., Ravasio, L., De Longis, P., ... & Nappa, S. (2001). Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *JAIDS Journal of Acquired Immune Deficiency Syndromes, 28*, 445-449.

An, S. F., Groves, M., Gray, F., & Scaravilli, F. (1999). Early entry and widespread cellular involvement of HIV-1 DNA in brains of HIV-1 positive asymptomatic individuals. *Journal of Neuropathology & Experimental Neurology, 58*, 1156-1162

Ances, B. M., & Ellis, R. J. (2007). Dementia and neurocognitive disorders due to HIV-1 infection. *Seminars in Neurology, 27,* 86-92.

Andrade, A. S., Deutsch, R., Celano, S., Duarte, N. A., Marcotte, T. D., Umlauf, A., ... & Collier, A. C. (2013). Relationships among neurocognitive status, medication adherence measured by pharmacy refill records, and virologic suppression in HIV-infected persons. *Journal of Acquired Immune Deficiency Syndromes*, *62*, 282-292.

Andrade, A. S., McGruder, H. F., Wu, A. W., Celano, S. A., Skolasky, R. L., Selnes, O. A., ... & McArthur, J. C. (2005). A programmable prompting device improves adherence to highly active antiretroviral therapy in HIV-infected subjects with memory impairment. *Clinical Infectious Diseases, 41*, 875-882.

Anthony, I. C., & Bell, J. E. (2008). The neuropathology of HIV/AIDS. *International Review of Psychiatry, 20,* 15-24.

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., … & Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology, 69,* 1789-1799.

Antiretroviral Therapy Cohort Collaboration (ART-CC). (2015). Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS, 29,* 373-383.

Arbuckle, J. L. (2016). Amos (Version 24.0) [Computer Program]. Chicago: IBM SPSS.

Arnsten, J. H., Demas, P. A., Farzadegan, H., Grant, R. W., Gourevitch, M. N., Chang, C. J., ... & Schoenbaum, E. E. (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clinical Infectious Diseases, 33,* 1417-1423.

Aronov, A., Rabin, L. A., Fogel, J., Chi, S. Y., Kann, S. J., Abdelhak, N., & Zimmerman, M. E. (2015). Relationship of cognitive strategy use to prospective memory performance in a diverse sample of nondemented older adults with varying degrees of cognitive complaints and impairment. *Aging, Neuropsychology, and Cognition, 22,* 486-501.

Bangsberg, D. R., Kroetz, D. L., & Deeks, S. G. (2007). Adherence-resistance relationships to combination HIV antiretroviral therapy. *Current HIV/AIDS Reports, 4*, 65-72.

Bangsberg, D. R., Perry, S., Charlebois, E. D., Clark, R. A., Roberston, M., Zolopa, A. R., & Moss, A. (2001). Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS, 15*, 1181-1183.

Barclay, T. R., Hinkin, C. H., Castellon, S. A., Mason, K. I., Reinhard, M. J., Marion, S. D., ... & Durvasula, R. S. (2007). Age-associated predictors of medication adherence in HIV-positive adults: health beliefs, self-efficacy, and neurocognitive status. *Health Psychology, 26*, 40-49.

Barker-Collo, S. L. (2003). Culture and validity of the Symptom Checklist-90-Revised and Profile of Mood States in a New Zealand student sample. *Cultural Diversity and Ethnic Minority Psychology, 9*, 185-196.

Barroso, J., Carlson, J. R., & Meynell, J. (2003). Physiological and psychological markers associated with HIV-related fatigue. *Clinical Nursing Research, 12*, 49-68.

Barroso, J., Leserman, J., Harmon, J. L., Hammill, B., & Pence, B. W. (2015). Fatigue in HIV-Infected people: a three-year observational study. *Journal of Pain and Symptom Management, 50*, 69-79.

Becker, J. T., Caldararo, R., Lopez, O. L., Dew, M. A., Dorst, S. K., & Banks, G. (1995). Qualitative features of the memory deficit associated with HIV infection and AIDS: Cross-validation of a discriminant function classification scheme. *Journal of Clinical and Experimental Neuropsychology, 17*, 134-142.

Becker, J. T., Maruca, V., Kingsley, L. A., Sanders, J. M., Alger, J. R., Barker, P. B., ... & Sacktor, N. (2012). Factors affecting brain structure in men with HIV disease in the post-HAART era. *Neuroradiology, 54*, 113-121.

Bellizzi, M. J., Lu, S. M., & Gelbard, H. A. (2006). Protecting the synapse: evidence for a rational strategy to treat HIV-1 associated neurologic disease. *Journal of Neuroimmune Pharmacology, 1*, 20-31.

Benedict, R. H., Mezhir, J. J., Walsh, K., & Hewitt, R. G. (2000). Impact of human immunodeficiency virus type-1-associated cognitive dysfunction on activities of daily living and quality of life. *Archives of Clinical Neuropsychology, 15*, 535-544.

Berger, P. J., McCutcheon, L., Soust, M., Walker, A. M., & Wilkinson, M. H. (1991). Electromyographic changes in the isolated rat diaphragm during the development of fatigue. *European Journal of Applied Physiology and Occupational Physiology, 62*, 310-316.

Bhaskaran, K., Hamouda, O., Sannes, M., Boufassa, F., Johnson, A. M., Lambert, P. C., ... & Cascade Collaboration. (2008). Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *Journal of the American Medical Association*, *300*, 51-59.

Binford, M. C., Kahana, S. Y., & Altice, F. L. (2012). A systematic review of antiretroviral adherence interventions for HIV-infected people who use drugs. *Current HIV/AIDS Reports*, *9*, 287-312.

Biswas, B., Spitznagel, E., Collier, A. C., Gelman, B. B., McArthur, J. C., Morgello, S., ... & The Charter Group. (2014). Characterizing HIV medication adherence for virologic success among individuals living with HIV/AIDS: Experience with the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort. *Journal of HIV/AIDS & Social Services*, *13*, 8-25.

Blackstone, K., Moore, D. J., & Woods, S. P. (2013). The role of secondary factors in HIV-associated neurocognitive disorders. In P. A. Arnett (Ed.), *Secondary influences on neuropsychological test performance*, (pp. 228-258). New York, NY: Oxford University Press.

Blackstone, K., Woods, S. P., Weber, E., Grant, I., Moore, D. J., & HNRP Group. (2013). Memory-based strategies for antiretroviral medication management: an evaluation of clinical predictors, adherence behavior awareness, and effectiveness. *AIDS and Behavior*, *17*, 74-85.

Breitbart, W., McDonald, M.V., Rosenfeld, B., Monkman, N. D., & Passik, S. (1998). Fatigue in ambulatory AIDS patients. *Journal of Pain and Symptom Management*, *15*, 159-167.

Bruce-Keller, A. J., Chauhan, A., Dimayuga, F. O., Gee, J., Keller, J. N., & Nath, A. (2003). Synaptic transport of human immunodeficiency virus-Tat protein causes neurotoxicity and gliosis in rat brain. *The Journal of Neuroscience*, *23*, 8417-8422.

Burdo, T. H., Weiffenbach, A., Woods, S. P., Letendre, S., Ellis, R. J., & Williams, K. C. (2013). Elevated sCD163 in plasma but not cerebrospinal fluid is a marker of neurocognitive impairment in HIV infection. *AIDS (London, England)*, *27*, 1-16.

Burkard, C., Rochat, L., Emmenegger, J., Juillerat Van der Linden, A. C., Gold, G., & Van der Linden, M. (2014). Implementation intentions improve prospective memory and inhibition performances in older adults: The role of visualization. *Applied Cognitive Psychology*, *28*, 640-652.

Camp, C. J., Foss, J. W., O'Hanlon, A. M., & Stevens, A. B. (1996). Memory interventions for persons with dementia. *Applied Cognitive Psychology, 10*, 193-210.

Carey, C. L., Woods, S. P., Rippeth, J. D., Heaton, R. K., & Grant, I., & The HNRC Group. (2006). Prospective memory in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology, 28*, 536–548.

Castellon, S. A., Hardy, D. J., Hinkin, C. H., Satz, P., Stenquist, P. K., van Gorp, W. G., ... & Moore, L. (2006). Components of depression in HIV-1 infection: their differential relationship to neurocognitive performance. *Journal of Clinical and Experimental Neuropsychology*, *28*, 420-437.

Castelo, J. M., Sherman, S. J., Courtney, M. G., Melrose, R. J., & Stern, C. E. (2006). Altered hippocampal-prefrontal activation in HIV patients during episodic memory encoding. *Neurology, 66*, 1688–1695.

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & McAuliffe, T. L. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychology, 19*, 124-133.

Centers for Disease Control and Prevention (CDC. (2011). Vital signs: HIV prevention through care and treatment--United States. *MMWR. Morbidity and Mortality Weekly Report*, *60*, 1618-1623.

Centers for Disease Control and Prevention (CDC). (2015a). *HIV Surveillance Report, 2014, 26*, 1-123. Published November 2015. Accessed [December 3rd, 2015].

Centers for Disease Control and Prevention (CDC). (2015b). Monitoring selected national HIV prevention and care objectives by using HIV surveillance data-United States and 6 dependent areas-2013. *HIV Surveillance Supplemental Report 2015*, *20*, 1-70. Published July 2015. Accessed [December 5th, 2015].

Chaudhuri, A., & Behan, P. O. (2004). Fatigue in neurological disorders. *The Lancet, 363*, 978-988.

Chesney, M. A., Ickovics, J. R., Chambers, D. B., Gifford, A. L., Neidig, J., Zwickl, B., Wu, A. W., & Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult

AIDS Clinical Trials Group (AACTG). (2000). Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. *AIDS Care, 12*, 255-266.

Chiao, S., Rosen, H. J., Nicolas, K., Wendelken, L. A., Alcantar, O., Rankin, K. P., ... & Valcour, V. (2013). Deficits in self-awareness impact the diagnosis of asymptomatic neurocognitive impairment in HIV. *AIDS Research and Human Retroviruses, 29*, 949-956.

Clare, L., & Jones, R. S. (2008). Errorless learning in the rehabilitation of memory impairment: a critical review. *Neuropsychology Review, 18*, 1-23

Cleary, P. D., Fowler, F. J.,Weissman, J., Massagli, M. P.,Wilson, I., Seage, G. R., Gatsonis, C., & Epstein, A. (1993). Health-related quality of life in persons with acquired immune deficiency syndrome. *Medical Care, 31*, 569-580.

Clifford, D. B., & Ances, B. M. (2013). HIV-associated neurocognitive disorder. *The Lancet Infectious Diseases, 13*, 976-986.

Cohen, M. S., Chen, Y. Q., McCauley, M., Gamble, T., Hosseinipour, M. C., Kumarasamy, N., ... & Fleming, T. R. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *New England Journal of Medicine, 365*, 493-505.

Cole, S. W., Kemeny, M. E., & Taylor, S. E. (1997). Social identity and physical health: accelerated HIV progression in rejection-sensitive gay men. *Journal of Personality and Social Psychology, 72*, 320-335.

Correia, S., Cohen, R., Gongvatana, A., Ross, S., Olchowski, J., Devlin, K., ... & Delamonte, S. (2013). Relationship of plasma cytokines and clinical biomarkers to memory performance in HIV. *Journal of Neuroimmunology, 265*, 117-123.

Cunningham, W. E., Shapiro, M. F., Hays, R. D., Dixon, W. J., Visscher, B. R., George, L., Ettl, M. K., & Beck, K. (1998). Constitutional symptoms and health-related quality of life in patients with symptomatic HIV disease. *American Journal of Medicine, 104*, 129-136.

Cysique, L. A., Deutsch, R., Atkinson, J. H., Young, C., Marcotte, T. D., Dawson, L., ... & Heaton, R. K. (2007). Incident major depression does not affect neuropsychological functioning in HIV-infected men. *Journal of the International Neuropsychological Society, 13*, 1-11.

Dalmida, S. G., Holstad, M. M., Fox, R., & Delaney, A. M. (2015). Depressive symptoms and fatigue as mediators of relationship between poor sleep factors and medication adherence in HIV-positive women. *Journal of Research in Nursing, 20*, 499-514.

Darko, D. F., McCutchan, J. A., Kripke, D. F., Gillin, J. C., & Golshan, S. (1992). Fatigue, sleep disturbance, disability, and indices of progression of HIV infection. *American Journal of Psychiatry, 149*, 514-520.

Dawes, S., Suarez, P., Casey, C. Y., Cherner, M., Marcotte, T. D., Letendre, S., Grant, I., Heaton, R. K., & the HNRC Group. (2008). Variable patterns of neuropsychological performance in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology, 30*, 613-626.

DeJesus, E., Herrera, G., Teofilo, E., Gerstoft, J., Buendia, C. B., Brand, J. D., ... & Lanier, E. R. (2004). Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clinical Infectious Diseases, 39*, 1038-1046.

de Olalla, P.G., Knobel, H., Carmono, A., Guelar, A., Jose, L.C., & Joan, C.A. (2002). Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes, 30*, 105-110.

Deeks, S. G., Smith, M., Holodniy, M., & Kahn, J. O. (1997). HIV-1 protease inhibitors: a review for clinicians. *Journal of the American Medical Association, 277*, 145-153.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *The California Verbal Learning Test* (2nd ed.). San Antonio, TX: The Psychological Corporation.

Delis, D. C., Peavy, G., Heaton, R., Butters, N., Salmon, D. P., Taylor, M., ... & Atkinson, J. H. (1995). Do patients with HIV-associated minor cognitive/motor disorder exhibit a “subcortical” memory profile? Evidence using the California Verbal Learning Test. *Assessment, 2*, 151-165.

Di Stefano, M., Sabri, F., & Chiodi, F. (2005). HIV-1 structural and regulatory proteins and neurotoxicity. *The Neurology of AIDS, 2,* 49-56.

Doyle, K., Loft, S., Morgan, E. E., Weber, E., Cushman, C., Johnston, E., … The HNRP Group. (2013). Prospective memory in HIV-associated neurocognitive disorders (HAND): The neuropsychological dynamics of time monitoring. *Journal of Clinical and Experimental Neuropsychology, 35,* 359-372.

Duran, S., Spire, B., Raffi, F., Walter, V., Bouhour, D., Journot, V., et al. (2001) Self-reported symptoms after initiation of a protease inhibitor in HIV-infected patients and their impact on adherence to HAART. *HIV Clinical Trials, 2,* 38–45.

Einstein, G. O., & McDaniel, M. A. (2005). Prospective memory: Multiple retrieval processes. *Current Directions in Psychological Science, 14,* 286-290.

Einstein, G. O., McDaniel, M. A., Thomas, R., Mayfield, S., Shank, H., Morrisette, N., & Breneiser, J. (2005). Multiple processes in prospective memory retrieval: factors determining monitoring versus spontaneous retrieval. *Journal of Experimental Psychology: General, 134,* 327-342.

Ellis, R. J., Calero, P., & Stockin, M. D. (2009). HIV infection and the central nervous system: a primer. *Neuropsychological Review, 19,* 144-151.

Ettenhofer, M. L., Foley, J., Castellon, S. A., & Hinkin, C. H. (2010). Reciprocal prediction of medication adherence and neurocognition in HIV/AIDS. *Neurology, 74,* 1217-1222.

Fama, R., Rosenbloom, M. J., Nichols, B. N., Pfefferbaum, A., & Sullivan, E. V. (2009). Working and Episodic Memory in HIV Infection, Alcoholism, and Their Comorbidity: Baseline and 1-Year Follow-Up Examinations. *Alcoholism: Clinical and Experimental Research, 33,* 1815-1824.

Faytell, M. P., Doyle, K. L., Naar-King, S., Outlaw, A. Y., Nichols, S. L., Casaletto, K. B., & Woods, S. P. (2015). Visualisation of future task performance improves naturalistic prospective memory for some younger adults living with HIV disease. *Neuropsychological Rehabilitation, In Press*.

Ferrando, S., Evans, S., Goggin, K., Sewell, M., Fishman, B., & Rabkin, J. (1998). Fatigue in HIV illness: relationship to depression, physical limitations, and disability. *Psychosomatic Medicine*, *60*, 759-764.

Field, A. (2011). Discovering statistics using SPSS. 3rd Edition. Sage Publications, Los Angeles, USA.

Fisher, J. D., Amico, K. R., Fisher, W. A., & Harman, J. J. (2008). The information-motivation-behavioral skills model of antiretroviral adherence and its applications. *Current HIV/AIDS Reports*, *5*, 193-203.

Fisher W.A., Amico, R., & Harman, J. J. (2006). An information-motivation-behavioral skills model of adherence to antiretroviral therapy. *Health Psychology, 25*, 462–473.

Francis, D. J., Schatschneider, C., & Carlson, C. D. (2000). Introduction to individual growth curve analysis. In Handbook of research in pediatric and clinical child psychology (pp. 51-73). Springer US.

Gardner, E. M., McLees, M. P., Steiner, J. F., del Rio, C., & Burman, W. J. (2011). The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clinical Infectious Diseases*, *52*, 793-800.

Gatanaga, H., Tsukada, K., Honda, H., Tanuma, J., Yazaki, H., Watanabe,T., Honda, M., Teruya, K., Kikuchi, Y., & Oka, S. (2009) Detection of HIV Type 1 Load by the Roche Cobas TaqMan Assay in Patients with Viral Loads Previously Undetectable by the Roche Cobas Amplicor Monitor. *Clinical Infectious Diseases, 48*, 260–262.

Gay, C. L., Zak, R. S., Lerdal, A., Pullinger, C. R., Aouizerat, B. E., & Lee, K. A. (2015). Cytokine polymorphisms and plasma levels are associated with sleep onset insomnia in adults living with HIV/AIDS. *Brain, Behavior, and Immunity*, *47*, 58-65.

Gelman, B. B., Lisinicchia, J. G., Morgello, S., Masliah, E., Commins, D., Achim, C. L., ... & Yiannoutsos, C. T. (2013). Neurovirological correlation with HIV-associated neurocognitive disorders and encephalitis in a HAART-era cohort. *Journal of Acquired Immune Deficiency Syndromes*, *62*, 487-495.

Gifford, A. L., Laurent, D. D., Gonzalez, V. M., Chesney, M. A., & Lorig, K. R. (1998). Pilot randomized trial of education to improve self-management skills of men with symptomatic HIV/AIDS. *JAIDS Journal of Acquired Immune Deficiency Syndromes, 18,* 136-144.

Gisslén, M., Price, R. W., & Nilsson, S. (2011). The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? *BMC Infectious Diseases, 11,* 356-359.

Gongvatana, A., Woods, S. P., Taylor, M. J., Vigil, O., Grant, I., & the HNRC Group. (2007). Semantic clustering inefficiency in HIV-associated dementia. *Journal of Neuropsychiatry and Clinical Neuroscience, 19,* 36-42.

Gonzalez, J. S., Batchelder, A. W., Psaros, C., & Safren, S. A. (2011). Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. *Journal of Acquired Immune Deficiency Syndromes, 58,* 1-13.

Gordon, L. L., Gharibian, D., Chong, K., & Chun, H. (2015). Comparison of HIV virologic failure rates between patients with variable adherence to three antiretroviral regimen types. *AIDS Patient Care and STDs, 29,* 384-388.

Gorman, A. A., Foley, J. M., Ettenhofer, M. L., Hinkin, C. H., & van Gorp, W. G. (2009). Functional consequences of HIV-associated neuropsychological impairment. *Neuropsychology Review, 19,* 186-203.

Goswami, U., Baker, J. V., Wang, Q., Khalil, W., & Kunisaki, K. M. (2015). Sleep Apnea Symptoms as a Predictor of Fatigue in an Urban HIV Clinic. *AIDS Patient Care and STDs, 29,* 591-596.

Gould, O. N., McDonald-Miszczak, L., & Gregory, J. (1999). Prediction accuracy and medication instructions: will you remember tomorrow? *Aging, Neuropsychology, and Cognition, 6,* 141-154.

Gould, O. N., McDonald-Miszczak, L., & King, B. (1997). Metacognition and medication adherence: how do older adults remember? *Experimental Aging Research, 23,* 315-342.

Grant, I., Franklin, D. R., Deutsch, R., Woods, S. P., Vaida, F., Ellis, R. J., ... & Heaton, R. K. (2014). Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology, 82,* 2055-2062.

Gunstad, J., Lhotsky, A., Wendell, C. R., Ferrucci, L., & Zonderman, A. B. (2010). Longitudinal examination of obesity and cognitive function: results from the Baltimore longitudinal study of aging. *Neuroepidemiology, 34*, 222-229.

Gupta, S., Paul Woods, S., Weber, E., Dawson, M. S., Grant, I., & HIV Neurobehavioral Research Center (HNRC) Group. (2010). Is prospective memory a dissociable cognitive function in HIV infection? *Journal of Clinical and Experimental Neuropsychology*, *32*, 898-908.

Hand, G. A., Phillips, K. D., & Dudgeon, W. D. (2006). Perceived stress in HIV-infected individuals: Physiological and psychological correlates. *AIDS Care, 18*, 1011-1017.

Hardy, H., Kumar, V., Doros, G., Farmer, E., Drainoni, M.L., Rybin, D., et al. (2011). Randomized controlled trial of a personalized cellular phone reminder system to enhance adherence to antiretroviral therapy. *AIDS Patient Care and STDS, 25*, 153–161.

Harrigan, P. R., Hogg, R. S., Dong, W. W., Yup, B., Wynhoven, B., Woodward, J., et al. (2005). Predictors of HIV drug-resistance mutations in a large antiretroviral-naïve cohort initiating triple antiretroviral therapy. *Journal of Infectious Diseases*, *191*, 339–347.

Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., ... & CHARTER Group. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy CHARTER Study. *Neurology*, *75*, 2087-2096.

Heaton, R. K., Franklin, D. R., Deutsch, R., Letendre, S., Ellis, R. J., Casaletto, K., ... & Teshome, M. (2015). Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *Clinical Infectious Diseases, 60*, 473-480.

Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., LeBlanc, S., ... & Grant, I. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *Journal of Neurovirology, 17*, 3-16.

Heaton, R. K., Grant, I., Butters, N., White, D. A., Kirson, D., Atkinson, J. H., ... & Abramson, I. (1995). The HNRC 500-Neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society*, *1*, 231-251.

Henderson, M., Safa, F., Easterbrook, P., & Hotopf, M. (2005). Fatigue among HIV-infected patients in the era of highly active antiretroviral therapy. *HIV Medicine*, *6*, 347-352.

Hinkin, C. H., Barclay, T. R., Castellon, S. A., Levine, A. J., Durvasula, R. S., Marion, S. D., ... & Longshore, D. (2007). Drug use and medication adherence among HIV-1 infected individuals. *AIDS and Behavior*, *11*, 185-194.

Hinkin, C. H., Castellon, S. A., Durvasula, R. S., Hardy, D. J., Lam, M. N., Mason, K. I., ... & Stefaniak, M. (2002). Medication adherence among HIV+ adults: Effects of cognitive dysfunction and regimen complexity. *Neurology*, *59*, 1944-1950.

Hinkin, C. H., Hardy, D. J., Mason, K. I., Castellon, S. A., Durvasula, R. S., Lam, M. N., & Stefaniak, M. (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS (London, England)*, *18*, S19-S.

Hinkin, C. H., van Gorp, W. G., Mandelkern, M. A., Gee, M., Satz, P., Hoiston, S., Marcotte, T. D., ... & Blahd, W. H. (1995). Cerebral metabolic change in patients with AIDS: report of a six-month follow-up using positron-emission tomography. *Neurosciences*, *7*, 180-187.

Hinkin, C. H., van Gorp, W. G., Satz, P., Marcotte, T., Durvasula, R. S., Wood, S., ... & Baluda, M. R. (1996). Actual versus self-reported cognitive dysfunction in HIV-1 infection: memory-metamemory dissociations. *Journal of Clinical and Experimental Neuropsychology*, *18*, 431-443.

HNRC Group, Dawes, S., Suarez, P., Casey, C. Y., Cherner, M., Marcotte, T. D., ... & Heaton, R. K. (2008). Variable patterns of neuropsychological performance in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology*, *30*, 613-626.

Hoare, J., Westgarth-Taylor, J., Fouche, J. P., Spottiswoode, B., Paul, R., Thomas, K., Stein, D., & Joska, J. (2012). A diffusion tensor imaging and neuropsychological study of prospective memory impairment in South African HIV positive individuals. *Metabolic Brain Disease*, *27*(3), 289-297.

Holmes, C. B., & Sanne, I. (2015). Changing models of care to improve progression through the HIV treatment cascade in different populations. *Current Opinion in HIV and AIDS, 10,* 447-450.

Holzemer, W. L., Corless, I. B., Nokes, K. M., Turner, J. G., Brown, M. A., Powell-Cope, G. M., ... & Portillo, C. J. (1999). Predictors of self-reported adherence in persons living with HIV disease. *AIDS Patient Care and STDs, 13,* 185-197.

Hult., B., Chana, G., Masliah, E., & Everall, I. (2008). Neurobiology of HIV. *International Review of Psychiatry, 20,* 3-13.

Impellizzeri, F. M., Agosti, F., De Col, A., & Sartorio, A. (2013). Psychometric properties of the Fatigue Severity Scale in obese patients. *Health and Quality of Life Outcomes*, *11*, 1-7.

Jacks, A., Wainwright, D. A., Salazar, L., Grimes, R., York, M., Strutt, A. M., ... & Hasbun, R. (2015). Neurocognitive deficits increase risk of poor retention in care among older adults with newly diagnosed HIV infection. *AIDS*, *29*, 1711-1714.

Jason, L. A., Evans, M., Brown, M., & Porter, N. (2010). What is fatigue? Pathological and nonpathological fatigue. *Physical Medicine & Rehabilitation, 2,* 327-331.

Jensen, K., Goo, Y. A., Yahiaoui, A., Bajwa, S., Goodlett, D., Russo, J., & Voss, J. (2014). Identification of fatigue biomarkers in treated and treatment-naive HIV patients: preliminary results. *Biological Research for Nursing, 16*, 278-287.

Johnson, M.O., Charlebois, E., Morin, S.F., Catz, S.L., Goldstein, R.B., Remien, R.H., . . . Chesney, M.A. (2005). Perceived adverse effects of antiretroviral therapy. *Journal of Pain and Symptom Management, 29,* 193-205.

Johnson, K. L., Bamer, A. M., Yorkston, K. M., & Amtmann, D. (2009). Use of cognitive aids and other assistive technology by individuals with multiple sclerosis. *Disability and Rehabilitation: Assistive Technology, 4*, 1-8.

Jones, B. & Sall, J. (2011). JMP statistical discovery software. *Wiley Interdisciplinary Reviews: Computational Statistics, 3,* 188-194.

Jong, E., Oudhoff, L. A., Epskamp, C., et al. (2010). Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. *AIDS, 24,* 1387-1405.

Kalichman, S. C., Cain, D., Cherry, C., Kalichman, M., & Pope, H. (2005). Pillboxes and antiretroviral adherence: prevalence of use, perceived benefits, and implications for electronic medication monitoring devices. *AIDS Patient Care & STDs, 19,* 833-839.

Kalechstein, A. D., Hinkin, C. H., van Gorp, W. G., Castellon, S. A., & Satz, P. (1998). Depression predicts procedural but not episodic memory in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology, 20,* 529-535.

Kalichman, S., Kalichman, M. O., & Cherry, C. (2015). Medication Beliefs and Structural barriers to Treatment Adherence Among People Living with HIV Infection. *Psychology & Health, In Press,* 1-25.

Kalichman S. C., Ramachandran, B., & Catz, S. (1999). Adherence to combination antiretroviral therapies in HIV patients of low health literacy. *Journal of General Internal Medicine, 14,* 267–273.

Kalichman, S. C., Rompa, D., & Cage, M. (2000). Distinguishing between overlapping somatic symptoms of depression and HIV disease in people living with HIV-AIDS. *The Journal of Nervous and Mental Disease, 188,* 662-670.

Karasi, J. C., Dziezuk, F., Quennery, L., Förster, S., Reischl, U., Colucci, G., ... & Schmit, J. C. (2011). High correlation between the Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1, v2. 0 and the Abbott m2000 RealTime HIV-1 assays for quantification of viral load in HIV-1 B and non-B subtypes. *Journal of Clinical Virology, 52,* 181-186.

Kennedy, S., Goggin, K., & Nollen, N. (2004). Adherence to HIV medications: Utility of the theory of self-determination. *Cognitive Therapy and Research, 28,* 611-628.

Klem, L. (1995). Chapter 3: Path analysis. In: Grimm, L. G., & Yarnold, P. R. (Eds.). *Reading and understanding multivariate statistics.* Washington, DC: American Psychological Association.

Kliegel, M., Jäger, T., & Phillips, L. H. (2008). Adult age differences in event-based prospective memory: A meta-analysis on the role of focal versus non-focal cues. *Psychology and Aging, 23,* 203–208.

Kliegel, M., MacKinlay, R. & Jager, T. (2008b). A life span approach to the development of complex prospective memory. In M. Kliegel, M. A. McDaniel and G. O. Einstein (eds.), *Prospective Memory: Cognitive, Neuroscience, Developmental, and Applied Perspectives*. London: Lawrence Erlbaum.

Kline, R. B. (2011). *Principles and practice of structural equation modeling*. 3rd edition. Guilford publications.

Koopman, J., Howe, M., Hollenbeck, J. R., & Sin, H. P. (2015). Small sample mediation testing: misplaced confidence in bootstrapped confidence intervals. *Journal of Applied Psychology, 100,* 194-202.

Krummenacher, I., Cavassini, M., Bugnon, O., & Schneider, M. P. (2011). An interdisciplinary HIV-adherence program combining motivational interviewing and electronic antiretroviral drug monitoring. *AIDS Care, 23,* 550-561.

Laprise, C., de Pokomandy, A., Baril, J. G., Dufresne, S., & Trottier, H. (2013). Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clinical Infectious Diseases, 57,* 1489-1496.

Lee, K. A., Hicks, G., & Nino-Murcia, G. (1990). Validity and reliability of a scale to assess fatigue. *Psychiatry Research, 36,* 291-298.

Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: an update. *Advances in Nursing Science, 19,* 14-27.

Leserman, J., Barroso, J., Pence, B. W., Salahuddin, N., & Harmon, J. L. (2008). Trauma, stressful life events and depression predict HIV-related fatigue. *AIDS Care, 20,* 1258-1265.

Levine, B., Robertson, I. H., Clare, L., Carter, G., Hong, J., Wilson, B. A., ... & Stuss, D. T. (2000). Rehabilitation of executive functioning: An experimental–clinical validation of goal management training. *Journal of the International Neuropsychological Society, 6,* 299-312.

Lewis, G., & Wessely, S. (1992). The epidemiology of fatigue: more questions than answers. *Journal of Epidemiology and Community Health, 46,* 92-97.

Lima, V. D., Geller, J., Bangsberg, D. R., Patterson, T. L., Daniel, M., & Kerr, T. (2007). The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART. *AIDS, 21,* 1175–1183.

Liu, H., Golin, C. E., Miller, L. G., Hays, R. D., Beck, C. K., Sanandaji, S., ... & Wenger, N. S. (2001). A comparison study of multiple measures of adherence to HIV protease inhibitors. *Annals of Internal Medicine, 134,* 968-977.

Loft, S., Doyle, K. L., Naar-King, S., Outlaw, A. Y., Nichols, S. L., Weber, E., ... & Woods, S. P. (2014). Allowing brief delays in responding improves event-based prospective memory for young adults living with HIV disease. *Journal of Clinical and Experimental Neuropsychology, 36,* 761-772.

Mahy, C. E., Moses, L. J., & Kliegel, M. (2014). The impact of age, ongoing task difficulty, and cue salience on preschoolers' prospective memory performance: The role of executive function. *Journal of Experimental Child Psychology, 127,* 52-64.

Martin, E. M., Nixon, H., Pitrack, D. L., Weddington, W., Rains, N. A., Nunnally, G., … Bechara, A. (2007). Characteristics of prospective memory deficits in HIV-seropositive substance-dependent individuals: Preliminary observations. *Journal of Clinical and Experimental Neuropsychology, 29,* 496–504.

Masliah, E., DeTeresa, R. M., Mallory, M. E., & Hansen, L. A. (2000). Changes in pathological findings at autopsy in AIDS cases for the last 15 years. *AIDS, 14,* 69-74.

Masliah, E., Heaton, R. K., Marcotte, T. D., Ellis, R. J., Wiley, C. A., Mallory, M., et al. (1997). Dendritic injury is a pathological substrate for human immunodeficiency virus-related cognitive disorders. *Annals of Neurology, 42,* 963–972.

Molassiotis, A., Nahas-Lopez, V., Chung, W. R., Lam, S. C., Li, C. P., & Lau, T. J. (2002). Factors associated with adherence to antiretroviral medication in HIV-infected patients. *International Journal of STD & AIDS, 13,* 301-310.

Morgan, E. E., Weber, E., Rooney, A. S., Grant, I., Woods, S. P., & HIV Neurobehavioral Research Program (HNRP) Group. (2012). Longer ongoing task delay intervals exacerbate prospective

memory deficits in HIV-associated neurocognitive disorders (HAND). *Journal of Clinical and Experimental Neuropsychology, 34,* 416-427.

McArthur, J. C., Brew, B. J., & Nath, A. (2005). Neurological complications of HIV infection. *The Lancet Neurology, 4,* 543-555.

McDonald-Miszczak, L., Maris, P., Fitzgibbon, T., & Ritchie , G. (2004). A pilot study examining older adults' beliefs related to medication adherence: The BERMA Survey. *Journal of Aging and Health, 16,* 591-614.

McIntosh, R. C., Rosselli, M., Uddin, L. Q., & Antoni, M. (2015). Neuropathological sequelae of Human Immunodeficiency Virus and apathy: A review of neuropsychological and neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 55,* 147-164.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1981). *Manual for the Profile of Mood States*. San Diego: Educational and Industrial Testing Service.

Meade, C. S., Conn, N. A., Skalski, L. M., & Safren, S. A. (2011). Neurocognitive impairment and medication adherence in HIV patients with and without cocaine dependence. *Journal of Behavioral Medicine, 34,* 128-138.

Meyer, A. C., Boscardin, W. J., Kwasa, J. K., & Price, R. W. (2013). Is it time to rethink how neuropsychological tests are used to diagnose mild forms of HIV-associated neurocognitive disorders? Impact of false-positive rates on prevalence and power. *Neuroepidemiology, 41,* 208-216.

Miller, L. G., Golin, C. E., Liu, H., Hays, R. D., Hua, J., Wenger, N. S., & Kaplan, A. H. (2004). No evidence of an association between transient HIV viremia ("blips") and lower adherence to the antiretroviral medication regimen. *Journal of Infectious Diseases, 189,* 1487-1496.

Millikin, C. P., Rourke, S. B., Halman, M. H., & Power, C. (2003). Fatigue in HIV/AIDS is associated with depression and subjective neurocognitive complaints but not neuropsychological functioning. *Journal of Clinical and Experimental Neuropsychology, 25,* 201-215.

Mira, J. A., Macías, J., Nogales, C., Fernández-Rivera, J., García-García, J. A., Ramos, A., & Pineda, J. A. (2002). Transient rebounds of low-level viraemia among HIV-infected patients under HAART are not associated with virological or immunological failure. *Antiviral Therapy, 7*, 251-256.

Mitchell, M. M., Robinson, A. C., Nguyen, T. Q., & Knowlton, A. R. (2015). Informal Caregiver Characteristics Associated with Viral Load Suppression Among Current or Former Injection Drug Users Living with HIV/AIDS. *AIDS and Behavior, 19*, 2117–2122.

Montoya, J. L., Umlauf, A., Abramson, I., Badiee, J., Woods, S. P., Atkinson, J. H., … & TMARC Group. (2013). Dynamic indices of methamphetamine dependence and HIV infection predict fluctuations in affective distress: A five-year longitudinal analysis. *Journal of Affective Disorders, 151,* 728-737.

Morgan, E. E., Iudicello, J. E., Cattie, J. E., Blackstone, K., Grant, I., Woods, S. P., & HIV Neurobehavioral Research Program (HNRP) Group. (2015). Neurocognitive impairment is associated with lower health literacy among persons living with HIV infection. *AIDS and Behavior, 19,* 166-177.

Moyle, G., Fletcher, C., Brown, H., Mandalia, S., & Gazzard, B. (2006). Changes in sleep quality and brain wave patterns following initiation of an efavirenz-containing triple antiretroviral regimen. *HIV Medicine, 7,* 243-247.

Murji, S., Rourke, S. B., Donders, J., Carter, S. L., Shore, D., & Rourke, B. P. (2003). Theoretically derived CVLT subtypes in HIV-1 infection: Internal and external validation. *Journal of the International Neuropsychological Society, 9*, 1-16.

Nachega, J. B., Parienti, J. J., Uthman, O. A., Gross, R., Dowdy, D. W., Sax, P. E., ... & Giordano, T. P. (2014). Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clinical Infectious Diseases, 58,* 1297-1307.

Neuenburg, J. K., Brodt, H. R., Herndier, B. G., Bickel, M., Bacchetti, P., Price, R. W., ... & Schlote, W. (2002). HIV-related neuropathology, 1985 to 1999: rising prevalence of HIV encephalopathy in

the era of highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes, 31*, 171-177.

Norcross, J. C., Guadagnoli, E., & Prochaska, J. O. (1984). Factor structure of the Profile of Mood States (POMS): two partial replications. *Journal of Clinical Psychology, 40,* 1270-1277.

Norman, S. E., Chediak, A. D., Kiel, M., & Cohn, M. A. (1990). Sleep disturbances in HIV-infected homosexual men. *AIDS, 4*, 775-782.

Nyenhuis, D. L., Yamamoto, C., Luchetta, T., Terrien, A., & Parmentier, A. (1999). Adult and geriatric normative data and validation of the profile of mood states. *Journal of Clinical Psychology*, *55*, 79-86.

Obermeit, L. C., Morgan, E. E., Casaletto, K. B., Grant, I., Woods, S. P., & HIV Neurobehavioral Research Center (HNRC) Group. (2015). Antiretroviral non-adherence is associated with a retrieval profile of deficits in verbal episodic memory. *The Clinical Neuropsychologist, 29*,197-213.

Osowiecki, D. M., Cohen, R. A., Morrow, K. M., Paul, R. H., Carpenter, C. C., Flanigan, T., & Boland, R. J. (2000). Neurocognitive and psychological contributions to quality of life in HIV-1 infected women. *AIDS, 14*, 1327-1332.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services (DHHS). Available at https://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (2016). *Accessed 18 May 2016.*

Patterson, K., Young, C., Woods, S. P., Vigil, O., Grant, I., & Atkinson, J. H. (2006). Screening for major depression in persons with HIV infection: the concurrent predictive validity of the Profile of Mood States Depression-Dejection Scale. *International Journal of Methods in Psychiatric Research, 15*, 75-82.

Peavy, G., Jacobs, D., Salmon, D. P., Butters, N., Delis, D. C., Taylor, M., ... & Atkinson, J. H. (1994). Verbal memory performance of patients with human immunodeficiency virus infection: Evidence of subcortical dysfunction. *Journal of Clinical and Experimental Neuropsychology, 16*, 508-523.

Pellowski, J. A., & Kalichman, S. C. (2015). Health behavior predictors of medication adherence among low health literacy people living with HIV/AIDS. *Journal of Health Psychology*, 1-11.

Petersen, M. L., Wang, Y., Van Der Laan, M. J., Guzman, D., Riley, E., & Bangsberg, D. R. (2007). Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis. *Clinical Infectious Diseases, 45*, 908-915.

Perdices, M., Dunbar, N., Grunseit, A., Hall, W., & Cooper, D. A. (1992). Anxiety, depression and HIV related symptomatology across the spectrum of HIV disease. *Australian and New Zealand Journal of Psychiatry, 26*, 560-566.

Perkins, D. O., Leserman, J., Stern, R. A., Baum, S. F., Liao, D., Golden, R. N., & Evans, D. L. (1995). Somatic symptoms and HIV infection: relationship to depressive symptoms and indicators of HIV disease. *The American Journal of Psychiatry*, *152*, 1776-1781.

Perry, C. M., & Faulds, D. (1997). Lamivudine. *Drugs, 53*, 657-680.

Phillips, K. D., Sowell, R. L., Rojas, M., Tavakoli, A., Fulk, L. J., & Hand, G. A. (2004). Physiological and psychological correlates of fatigue in HIV disease. *Biological Research for Nursing, 6*, 59-74.

Piper, B. F. (1989). Fatigue: current bases for practice. In: *Management of Pain, Fatigue and Nausea* (pp. 187-198). Macmillan Education UK.

Podsadecki, T. J., Vrijens, B. C., Tousset, E. P., Rode, R. A., & Hanna, G. J. (2007). Decreased adherence to antiretroviral therapy observed prior to transient human immunodeficiency virus type 1 viremia. *Journal of Infectious Diseases*, *196*, 1773-1778.

Poquette, A. J., Moore, D. J., Gouaux, B., Morgan, E. E., Grant, I., & Woods, S. P. (2013). Prospective memory and antiretroviral medication non-adherence in HIV: an analysis of ongoing task delay

length using the memory for intentions screening test. *Journal of the International Neuropsychological Society, 19,* 155-161.

Powderly, W. G. (2002). Sorting through confusing messages: the art of HAART. *Journal of Acquired Immune Deficiency Syndromes, 31,* S3–S9.

Psychological Corporation. (1997). *WAIS-III and WMS-III technical manual.* San Antonio, TX: Psychological Corporation.

Psychological Corporation. (2001). *Wechsler Test of Adult Reading.* San Antonio, TX: Psychological Corporation.

Raboud, J. M., Rae, S., Woods, R., Harris, M., & Montaner, J. S. (2002). Consecutive rebounds in plasma viral load are associated with virological failure at 52 weeks among HIV-infected patients. *AIDS, 16,* 1627-1632.

Rabkin, J. G., Ferrando, S. J., van Gorp, W., Rieppi, R., McElhiney, M., & Sewell, M. (2000). Relationships among apathy, depression, and cognitive impairment in HIV/AIDS. *The Journal of Neuropsychiatry and Clinical Neurosciences, 12,* 451-457.

Raskin, S. (2004). Memory for intentions screening test [abstract]. *Journal of the International Neuropsychological Society, 10,* 110.

Raskin, S., Buckheit, C., & Sherrod, C. (2010). MIST Memory for Intentions Test professional manual. *Lutz, FL: Psychological Assessment Resources*.

Reddon, J. R., Marceau, R., & Holden, R. R. (1985). A confirmatory evaluation of the Profile of Mood States: Convergent and discriminant item validity. *Journal of Psychopathology and Behavioral Assessment,* 243-259.

Reger, M., Welsh, R., Razani, J., Martin, D. J., & Boone, K. B. (2002). A meta-analysis of the neuropsychological sequelae of HIV infection. *Journal of the International Neuropsychological Society, 8,* 410-424.

Rippeth, J. D., Heaton, R. K., Carey, C. L., Marcotte, T. D., Moore, D. J., Gonzalez, R., ... & HNRC group. (2004). Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. *Journal of the International Neuropsychological Society*, *10*, 1-14.

Robertson, K. R., Smurzynski, M., Parsons, T. D., Wu, K., Bosch, R. J., Wu, J., ... & Ellis, R. J. (2007). The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*, *21*, 1915-1921.

Robinson-Papp, J., Byrd, D., Mindt, M. R., Oden, N. L., Simpson, D. M., & Morgello, S. (2008). Motor function and human immunodeficiency virus–associated cognitive impairment in a highly active antiretroviral therapy–era cohort. *Archives of Neurology*, *65*, 1096-1101.

Rodrigues, D., Tran, Y., Wijesuriya, N., Guest, R., Middleton, J., & Craig, A. (2013). Pain intensity and its association with negative mood states in patients with spinal cord injury. *Pain Therapy*, *2*, 113-119.

Ruelle, J., Debaisieux, L., Vancutsem, E., De Bel, A., Delforge, M. L., Piérard, D., & Goubau, P. (2012). HIV-1 low-level viraemia assessed with 3 commercial real-time PCR assays show high variability. *BMC Infectious Diseases*, *12*, 1-6.

Rumbaugh, J. A., & Nath, A. (2006). Developments in HIV neuropathogenesis. *Current Pharmaceutical Design*, *12*, 1023-1044.

Ryscavage, P., Kelly, S., Li, J. Z., Harrigan, P. R., & Taiwo, B. (2014). Significance and clinical management of persistent low level viremia and very low level viremia in HIV-1 infected patients. *Antimicrobial Agents and Chemotherapy*, *58*, 3585-3598.

Sacktor, N., Lyles, R. H., Skolasky, R., Kleeberger, C., Selnes, O. A., Miller, E. N., et al. (2001). HIV-associated neurologic disease incidence changes: multicenter AIDS cohort study, 1990–1998. *Neurology*, *56*, 257–260.

Safren, S. A., Hendriksen, E. S., Desousa, N., Boswell, S. L., & Mayer, K. H. (2003). Use of an on-line pager system to increase adherence to antiretroviral medications. *AIDS Care*, *15*, 787-793.

Safren, S. A., Otto, M. W., Worth, J. L., Salomon, E., Johnson, W., Mayer, K., & Boswell, S. (2001). Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behaviour Research and Therapy, 39*, 1151-1162.

Salahuddin, N., Barroso, J., Leserman, J., Harmon, J. L., & Pence, B. W. (2009). Daytime sleepiness, nighttime sleep quality, stressful life events, and HIV-related fatigue. *Journal of the Association of Nurses in AIDS Care, 20*, 6-13.

Samji, H., Cescon, A., Hogg, R. S., Modur, S. P., Althoff, K. N., Buchacz, K., ... & Gange, S. J. (2013). Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS ONE, 8*, 1-8.

Sax, P. E., Meyers, J. L., Mugavero, M., & Davis, K. L. (2012). Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. *PLoS One, 7*, 1-9.

Schnitzspahn, K. M., Ihle, A., Henry, J. D., Rendell, P. G., & Kliegel, M. (2011). The age-prospective memory paradox: an exploration of possible mechanisms. *International Psychogeriatrics, 23,* 583-592.

Scott, J. C., Woods, S. P., Patterson, K. A., Morgan, E. E., Heaton, R. K., Grant, I., ... & HIV Neurobehavioral Research Center (HNRC) Group. (2006). Recency effects in HIV-associated dementia are characterized by deficient encoding. *Neuropsychologia, 44*, 1336-1343.

Sewell, M. C., Goggin, K. J., Rabkin, J. G., Ferrando, S. J., McElhiney, M. C., & Evans, S. (2000). Anxiety syndromes and symptoms among men with AIDS: a longitudinal controlled study. *Psychosomatics, 41*, 294-300.

Siegel, K., Schrimshaw, E. W., & Raveis, V. H. (2000). Accounts for non-adherence to antiviral combination therapies among older HIV-infected adults. *Psychology, Health & Medicine, 5*, 29-42.

Sin, N. L., & DiMatteo, M. R. (2014). Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. *Annals of Behavioral Medicine, 47*, 259-269.

Sheppard, D. P., Weber, E., Casaletto, K. B., Avci, G., Woods, S. P., Grant, I., ... & Marquie-Beck, J. (2016). Pill Burden Influences the Association Between Time-Based Prospective Memory and Antiretroviral Therapy Adherence in Younger But Not Older HIV-Infected Adults. *Journal of the Association of Nurses in AIDS Care, In Press,* 1-13.

Sheppard, D. P., Woods, S. P., Bondi, M. W., Gilbert, P. E., Massman, P. J., & Doyle, K. L. (2015). Does older age confer an increased risk of incident neurocognitive disorders among persons living with HIV disease? *The Clinical Neuropsychologist, 29,* 656-677.

Shi, L., Liu, J., Fonseca, V., Walker, P., Kalsekar, A., & Pawaskar, M. (2010). Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. *Health and Quality of Life Outcomes, 8,* 1-7.

Smith, G. V., Della Sala, S., Logie, R. H., & Maylor, E. A. M. (2000). Prospective and retrospective memory in normal aging and dementia: a questionnaire study. *Memory, 8,* 311-321.

Sowa, N. A., Bengtson, A., Gaynes, B. N., & Pence, B. W. (2016). Predictors of depression recovery in HIV-infected individuals managed through measurement-based care in infectious disease clinics. *Journal of Affective Disorders, 192,* 153-161.

StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

Strober, L. B. & DeLuca, J. (2013). Fatigue: its influence on cognition and assessment. In P. A. Arnett (Ed.), *Secondary influences on neuropsychological test performance* (pp. 117-141). New York, NY: Oxford University Press.

Sturdevant, C. B., Joseph, S. B., Schnell, G., Price, R. W., Swanstrom, R., & Spudich, S. (2015). Compartmentalized replication of R5 T cell-tropic HIV-1 in the central nervous system early in the course of infection. *PLoS Pathogens, 11,* 1-16.

Swain, M. G. (2000). Fatigue in chronic disease. *Clinical Science, 99,* 1-8.

Swenson, L. C., Cobb, B., Geretti, A. M., Harrigan, P. R., Poljak, M., Seguin-Devaux, C., ... & Wensing, A. M. (2014). Comparative performances of HIV-1 RNA load assays at low viral load levels: results of an international collaboration. *Journal of Clinical Microbiology, 52,* 517-523.

Tello-Velásquez, J. R., Díaz-Llanes, B. E., Mezones-Holguín, E., Rodríguez-Morales, A. J., Huamaní, C., Hernández, A. V., & Arévalo-Abanto, J. (2015). Poor quality of sleep associated with low adherence to highly active antiretroviral therapy in Peruvian patients with HIV/AIDS. *Cadernos de Saúde Pública, 31*, 989-1002.

Thames, A. D., Kim, M. S., Becker, B. W., Foley, J. M., Hines, L. J., Singer, E. J., ... & Hinkin, C. H. (2011). Medication and finance management among HIV-infected adults: The impact of age and cognition. *Journal of Clinical and Experimental Neuropsychology, 33*, 200-209.

Thames, A. D., Arentoft, A., Rivera-Mindt, M., & Hinkin, C. H. (2013). Functional disability in medication management and driving among individuals with HIV: a 1-year follow-up study. *Journal of Clinical and Experimental Neuropsychology, 35*, 49-58.

Trotta, M. P., Ammassari, A., Cozzi-Lepri, A., Zaccarelli, M., Castelli, F., Narciso, P., ... & Antinori, A. (2003). Adherence to highly active antiretroviral therapy is better in patients receiving non-nucleoside reverse transcriptase inhibitor-containing regimens than in those receiving protease inhibitor-containing regimens. *AIDS, 17*, 1099-1102.

van Gorp, W. G. (2008). Neuropsychiatric predictors of return to work in HIV infection; Presentation at the American Psychological Association 116th Annual Convention; Boston, Massachusetts.

van Gorp, W. G., Baerwald, J. P., Ferrando, S., McElhiney, M. C., & Rabkin, J. G. (1999). The relationship between employment and neuropsychological impairment in HIV infection. *Journal of the International Neuropsychological Society, 5*, 534–539.

van Gorp, W. G., Rabkin, J. G., Ferrando, S. J., Mintz, J., Ryan, E., Borkowski, T., & Mcelhiney, M. (2007). Neuropsychiatric predictors of return to work in HIV/AIDS. *Journal of the International Neuropsychological Society, 13*, 80-89.

Vassallo, M., Durant, J., Biscay, V., Lebrun-Frenay, C., Dunais, B., Laffon, M., ... & Pradier, C. (2014). Can high central nervous system penetrating antiretroviral regimens protect against the onset of HIV-associated neurocognitive disorders? *AIDS, 28*, 493-501.

Viswanathan, S., Detels, R., Mehta, S. H., Macatangay, B. J., Kirk, G. D., & Jacobson, L. P. (2015). Level of Adherence and HIV RNA Suppression in the Current Era of Highly Active Antiretroviral Therapy (HAART). *AIDS and Behavior, 19,* 601-611.

Voss, J. G. (2005). Predictors and correlates of fatigue in HIV/AIDS. *Journal of Pain and Symptom Management, 29,* 173-184.

Wagner, G., Kanouse, D., Golinelli, D., et al. (2006). Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial. *AIDS, 20,* 1295–1302.

Walmsley, S. L., Antela, A., Clumeck, N., Duiculescu, D., Eberhard, A., Gutiérrez, F., ... & Pappa, K. (2013). Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. *New England Journal of Medicine, 369,* 1807-1818.

Watkins, C. C., & Treisman, G. J. (2015). Cognitive impairment in patients with AIDS–prevalence and severity. *HIV/AIDS – Research and Palliative Care, 7,* 35-47.

Weber, E., Morgan, E. E., Iudicello, J. E., Blackstone, K., Grant, I., Ellis, R. J., … & Moore, D. J. (2013). Substance use is a risk factor for neurocognitive deficits and neuropsychiatric distress in acute and early HIV infection. *Journal of Neurovirology, 19,* 65-74.

Weber, E., Woods, S. P., Delano-Wood, L., Bondi, M. W., Gilbert, P. E., Grant, I., & HIV Neurobehavioral Research Program (HNRP) Group. (2011). An examination of the age-prospective memory paradox in HIV-infected adults. *Journal of Clinical and Experimental Neuropsychology, 33,* 1108-1118.

White, J. L., Mitler, M. M., & Darko, D. F. (1995). Sleep disturbance in early HIV infection. *Focus, 10,* 5–6.

Wilson, N. L., Azuero, A., Vance, D. E., Richman, J. S., Moneyham, L. D., Raper, J. L., ... & Kempf, M. C. (2016). Identifying symptom patterns in people living with HIV disease. *Journal of the Association of Nurses in AIDS* Care, 27, 121-132.

Woods, S. P., Carey, C. L., Moran, L. M., Dawson, M. S., Letendre, S. L., Grant, I., & HIV Neurobehavioral Research Center (HNRC) Group. (2007a). Frequency and predictors of self-

reported prospective memory complaints in individuals infected with HIV. *Archives of Clinical Neuropsychology*, *22*, 187-195.

Woods, S. P., Dawson, M. S., Weber, E., Gibson, S., Grant, I., Atkinson, J. H., & The HNRC Group. (2009a). Timing is everything: Antiretroviral non-adherence is associated with impairment in time-based prospective memory. *Journal of the International Neuropsychological Society, 15*, 42-52.

Woods, S. P., Doyle, K. L., Morgan, E. E., Naar-King, S., Outlaw, A. Y., Nichols, S. L., & Loft, S. (2014). Task importance affects event-based prospective memory performance in adults with HIV-associated neurocognitive disorders and HIV-infected young adults with problematic substance use. *Journal of the International Neuropsychological Society, 20*, 652-662.

Woods, S. P., Iudicello, J., Moran, L. M., Carey, C. L., Dawson, M. S., Grant, I., & HIV Neurobehavioral Research Center (HNRC) group. (2008a). HIV-associated prospective memory impairment increases risk of dependence in everyday functioning. *Neuropsychology, 22*, 110-117.

Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009b). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychological Review, 19,* 152-168.

Woods, S. P., Moran, L. M., Carey, C. L., Dawson, M. S., Iudicello, J. E., Gibson, S., ... & HIV Neurobehavioral Research Center (HNRC) group. (2008b). Prospective memory in HIV infection: Is "remembering to remember" a unique predictor of self-reported medication management? *Archives of Clinical Neuropsychology, 23*, 257-270.

Woods, S. P., Moran, L. M., Dawson, M. S., Carey, C. L., Grant, I., & HIV Neurobehavioral Research Center (HNRC) Group. (2008c). Psychometric characteristics of the memory for intentions screening test. *The Clinical Neuropsychologist, 22*, 864-878.

Woods, S. P., Morgan, E. E., Marquie-Beck, J., Carey, C. L., Grant, I., & Letendre, S. L. (2006). Markers of macrophage activation and axonal injury are associated with prospective memory in HIV-1 disease. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology, 19*, 217-221.

Woods, S. P., Rippeth, J. D., Frol, A. B., Levy, J. K., Ryan, E., Soukup,V. M., et al. (2004). Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. *Journal of Clinical and Experimental Neuropsychology, 26,* 759–778.

Woods, S. P., Scott, J. C., Dawson, M. S., Morgan, E. E., Carey, C. L., Heaton, R. K., ... & HIV Neurobehavioral Research Center (HNRC) Group. (2005). Construct validity of Hopkins Verbal Learning Test—Revised component process measures in an HIV-1 sample. *Archives of Clinical Neuropsychology, 20*, 1061-1071.

Woods, S. P., Twamley, E. W., Dawson, M. S., Narvaez, J. M., & Jeste, D. V. (2007b). Deficits in cue detection and intention retrieval underlie prospective memory impairment in schizophrenia. *Schizophrenia Research, 90,* 344-350.

Woods, S. P., Weber, E., Weisz, B. M., Twamley, E. W., & Grant, I. (2011). Prospective memory deficits are associated with unemployment in persons living with HIV infection. *Rehabilitation Psychology, 56*, 77-84.

World Health Organization. Composite international diagnostic interview. World Health Organization; Geneva, Switzerland: 1998. (CIDI, version 2.1)

Wu, Y., Storey, P., Cohen, B. A., Epstein, L. G., Edelman, R. R., & Ragin, A. B. (2006). Diffusion alterations in corpus callosum of patients with HIV. *American Journal of Neuroradiology, 27,* 656-660.

Wu, J., Wu, H., Lu, C., Guo, L., & Li, P. (2015). Self-reported sleep disturbances in HIV-infected people: a meta-analysis of prevalence and moderators. *Sleep Medicine, 16,* 901-907.

Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management, 13,* 63-74.

Young, J., Rickenbach, M., Calmy, A., Bernasconi, E., Staehelin, C., Schmid, P., ... & Bucher, H. C. (2015). Transient detectable viremia and the risk of viral rebound in patients from the Swiss HIV Cohort Study. *BMC Infectious Diseases, 15*, 382-390.

Zeintl, M., Kliegel, M., Rast, P., & Zimprich, D. (2006). Prospective memory complaints can be predicted by prospective memory performance in older adults. *Dementia and Geriatric Cognitive Disorders*, *22*, 209-215.

Zogg, J. B., Woods, S. P., Sauceda, J. A., Wiebe, J. S., & Simoni, J. M. (2012). The role of prospective memory in medication adherence: a review of an emerging literature. *Journal of Behavioral Medicine, 35,* 47-62.

Zogg, J. B., Woods, S. P., Weber, E., Doyle, K., Grant, I., & The HNRP Group. (2011). Are time- and event-based prospective memory comparably affected in HIV infection? *Archives of Clinical Neuropsychology, 26*, 250–259.

## TABLES AND FIGURES

**Table 1.** Clinicodemographic characteristics of the overall sample at baseline.

| ***Characteristic (N=177)*** | ***Mean (SD)*** | ***# Missing (%)*** |
|---|---|---|
| **Demographics** | | |
| Age (years) | 48.6 (11.2) | 0 |
| Education (years) | 13.6 (2.6) | 0 |
| Estimated verbal IQ (WTAR reading) | 102.5 (11.8) | 0 |
| Sex (% male) | 85.9% | 0 |
| Ethnicity (%) | | 0 |
| Caucasian | 62.7% | |
| African-American | 22.0% | |
| Hispanic | 14.7% | |
| Native American | 0.5% | |
| **HAND Diagnosis (%)[a]** | 30.51% | 0 |
| **Global Clinical Rating Scores** | 3.93 (1.5) | 0 |
| **Neuropsychiatric Diagnoses (current or lifetime; %)[b]** | | |
| Major Depressive Disorder | 51.4% | 0 |
| Generalized Anxiety Disorder | 11.9% | 1 (0.6%) |
| Substance Use Disorders (lifetime only) | 74.0% | 0 |

***Notes.*** [a]Determined using the global clinical rating scores (Woods et al., 2004). [b]Based on the Composite International Diagnostic Interview (CIDI version 2.1; World Health Organization, 1998). WTAR: Wechsler Test of Adult Reading (Psychological Corporation, 2001).

**Table 2**. HIV disease and treatment characteristics of the overall sample at baseline.

| ***HIV Disease Characteristics (N=177)*** | ***Mean (SD)*** | ***# Missing (%)*** |
|---|---|---|
| **Estimated duration of infection (mos.)** | 182.0 (89.4) | 15 (8.5%) |
| **Nadir CD4 T-cell count (cells/µl)** | 178.1 (146.0) | 1 (0.6%) |
| **Current CD4 T-cell count (cells/µl)** | 543.3 (265.6) | 2 (1.1%) |
| **AIDS status (% AIDS)** | 66.7% | 0 |
| **Plasma HIV RNA** | | 1 (0.6%) |
| % Detectable | 15.8% | |
| % Undetectable | 84.2% | |
| **Most common ARTs** | | 1 (0.6%) |
| Tenofovir (TDF) | 139 (78.5%) | |
| Emtricitabine (FTC) | 117 (66.1%) | |
| Ritonavir (RTV) | 101 (57.1%) | |
| **Common elements of cART regimens:** | | 1 (0.6%) |
| FTC/RTV/ TDF | 66 (37.3%) | |
| FTC/RTV/TDF plus Atazanavir (ATV) | 28 (15.8%) | |
| FTC/RTV/TDF plus Lopinavir (LPV) | 12 (6.8%) | |
| Efavirenz (EFV)/FTC/TDF | 29 (16.4%) | |
| Nevirapine (NVP)/FTC/TDF | 8 (4.5%) | |
| Other elements: | 82 (46.3%) | |
| Other nucleoside reverse transcriptase inhibitors | 53 (29.9%) | |
| Other protease inhibitors | 37 (20.9%) | |
| Non-nucleoside reverse transcriptase inhibitors | 12 (6.8%) | |
| **# ARV Medications** | 3.4 (0.9) | 0 |
| **ARV Pill Burden (% High)** [a] | 41.2% | 0 |
| **# Non-ARV Medications** | 4.3 (4.2) | 0 |
| **Non-ARV Pill Burden (% High)** [a] | 48.6% | 0 |
| **# All Medications** | 7.7 (4.4) | 0 |
| **Total Med Burden (ARV + non-ARV)**[a] | 42.9% | 0 |

***Notes.*** [a]Based on a sample-based median split. Median for ARV medications = 3; median for Non-ARV medications = 3; median for all medications = 7. Participants with more than the median number of prescribed medications had "high" pill burden for each category. ARV: Antiretroviral. ATV: atazanavir. EFV: efavirenz. FTC: emtricitabine. LPV: lopinavir. RTV: ritonavir. TDF: tenofovir.

**Table 3**. Experimental characteristics of the overall sample at baseline.

| *Characteristic (N=177)* | *Mean (SD)* | *# Missing (%)* |
|---|---|---|
| **Adherence** | | |
| cART Adherence (BERMA MMES)[a] | 77.7 (13.4) | 1 (0.6%) |
| cART Adherence (ACTG; %)[b] | 98.8 (5.1) | 8 (4.5%) |
| Percent Adherent (>90; ACTG) | 94.7% | 8 (4.5%) |
| cART Adherence (MEMS; %)[c] | 86.1 (21.6) | 0 |
| Percent Adherent (>90; MEMS) | 66.1% | 0 |
| **Memory** | | |
| Retrospective Memory (CVLT-II)[a] | 10.1 (3.9) | 1 (0.6%) |
| Retrospective Memory (LM II)[a] | 24.7 (9.0) | 0 |
| Prospective Memory (MIST-15)[a] | 5 (1.8) | 0 |
| Prospective Memory (MIST-24) [a] | 0.6 (0.8) | 0 |
| **Fatigue (POMS-FI)[a]** | 8.2 (6.7) | 0 |
| **Compensatory Strategy Use (PMMQ)[a]** | 28.8 (16.3) | 16 (9.0%) |
| **Depression (POMS-DD)[a]** | 9.9 (10.8) | 0 |

***Notes***. [a]Presented as raw scores. [b]Calculated by 1 – (#pills skipped per day/#pills prescribed) averaged over four days and multiplied by 100. [c]Calculated by dividing actual dosing events by the number of prescribed doses and multiplying by 100. Data are presented as means and standard deviations or 95% confidence intervals except where indicated. ACTG: NIAID AIDS Clinical Trials Group Adherence to Anti-HIV Medications (4 days). BERMA MMES: Beliefs Related to cART Adherence, Medication Management Efficiency Scale. CVLT-II: California Verbal Learning Test – Second edition delayed free recall score. LM II: Logical Memory delayed free recall score from the Wechsler Memory Scale III. MEMS: Medication event monitoring system. MIST-15: Memory for Intentions Screening Test, long delay trial. MIST-24: Memory for Intentions Screening Test, 24-hour trial. PMMQ: Prospective Memory for Medications Questionnaire. POMS-FI: The Profile of Mood States, Fatigue-Inertia subscale. POMS-DD: The Profile of Mood States, Depression-Dejection subscale.

**Table 4**. Pre- and post-imputation means and standard deviations for variables with more than five percent of missing variables.

| | | | Pre-Imputation | | | Post-Imputation | | |
|---|---|---|---|---|---|---|---|---|
| | Variable | # Missing (%) | Percent | Mean (SD) | Range | Percent | Mean (SD) | Range |
| **AIM 1** (N = 177) | PMMQ | 16 (9.0%) | | 28.78 (16.33) | 0 - 69 | | 28.64 (15.78) | 0 - 69 |
| | Duration of HIV Infection (mos.) | 15 (8.5%) | | 181.96 (89.43) | 10.26 – 329.72 | | 180.95 (86.7) | 10.26 – 329.72 |
| **AIM 2** (N = 57) | Current Substance Use T2 | 3 (5.3%) | 5.6% | | 0 - 1 | 5.3% | | -.04 – 1 |
| | ACTG T2 | 3 (5.3%) | | 98.1 (8.2) | 50 – 100 | | 98.2 (8.0) | 50 – 102.5 |

***Note***. ACTG: NIAID AIDS Clinical Trials Group Adherence to Anti-HIV Medications (4 days). PMMQ: Prospective Memory for Medications Questionnaire. T2: time 2.

**Table 5**. Pattern of missing data for the overall sample at baseline.

| Count | # Columns missing | GAD | Duration of HIV Infection | Nadir CD4 | Current CD4 | Plasma HIV RNA | Current cART Regimen | BERMA MMES | MEMS ACTG | MEMS Duration (days) | MEMS PMMQ | CVLT-II |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 146 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| 4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 |
| 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 | 2 | 0 | 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 11 | 0 |
| 1 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 1 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total:** | **11** | **1** | **15** | **1** | **2** | **1** | **1** | **1** | **8** | **1** | **16** | **1** |

***Note.*** Light gray indicates 1-2 repeats of missing variable patterns, while dark gray indicates 4 or more repeats of missing variable patterns. ACTG: NIAID AIDS Clinical Trials Group Adherence to Anti-HIV Medications (4 days). GAD: generalized anxiety disorder (current or lifetime). BERMA MMES: Beliefs Related to cART Adherence, Medication Management Efficiency Scale. CVLT-II: California Verbal Learning Test – II. MEMS: medication event monitoring system. PMMQ: Prospective Memory for Medications Questionnaire.

**Table 6**. Clinicodemographic characteristics of the longitudinal sample at baseline and at one-year follow-up.

| | ***Baseline*** | | | | ***Follow-up*** | |
|---|---|---|---|---|---|---|
| ***Characteristics*** | ***Full Sample (N=177)*** | ***# Missing (%)*** | ***Long. Sample (N=57)*** | ***# Missing (%)*** | ***Long. Sample (N=57)*** | ***# Missing (%)*** |
| **Time of Evaluation (days; *mean (SD)*)** | 0 | 0 | 0 | 0 | 422.3 (65.4) | 0 |
| **Demographics** | | | | | | |
| Age (years; *mean (SD)*) | 48.6 (11.2) | 0 | 52.2 (10.7) | 0 | 53.4 (10.7) | 0 |
| Education (years; *mean (SD)*) | 13.6 (2.6) | 0 | 14.2 (2.7) | 0 | | |
| Estimated verbal IQ (WTAR reading; *mean (SD)*) | 102.5 (11.8) | 0 | 101 (11.8) | 0 | | |
| Sex (% male) | 85.9% | 0 | 82.5% | 0 | | |
| Ethnicity (%) | | 0 | | 0 | | |
| Caucasian | 62.7% | | 63.1% | | | |
| African-American | 22.0% | | 21.1% | | | |
| Hispanic | 14.7% | | 14.0% | | | |
| Native American | 0.5% | | 1.8% | | | |
| **Neuropsychiatric Diagnoses (current or lifetime; %)[a]** | | | | | | |
| Major Depressive Disorder | 51.4% | 0 | 52.6% | 0 | 63.2% | 0 |
| Generalized Anxiety Disorder | 11.9% | 1 (0.6%) | 12.3% | 0 | 21.1% | 0 |
| Substance Use Disorders (lifetime only) | 74.0% | 0 | 71.9% | 0 | 77.2% | 0 |
| Substance Use Disorders (current only) | 0% | 0 | 0% | 0 | 5.6% | 3 (5.3%) |
| Positive Urine Toxicology Screen | 0% | 0 | 0% | 0 | 17.5% | 0 |

***Notes.*** [a]Based on the Composite International Diagnostic Interview (CIDI version 2.1; World Health Organization, 1998). WTAR: Wechsler Test of Adult Reading (Psychological Corporation, 2001).

**Table 7**. HIV disease characteristics of the longitudinal sample at baseline and at one-year follow-up.

| | ***Baseline*** | | | | ***Follow-up*** | |
|---|---|---|---|---|---|---|
| ***HIV Disease Characteristics*** | ***Full Sample (N=177)*** | ***# Missing (%)*** | ***Long. Sample (N=57)*** | ***# Missing (%)*** | ***Long. Sample (N=57)*** | ***# Missing (%)*** |
| **Estimated duration of infection (mos.; *mean (SD)*)** | 182.0 (89.4) | 15 (8.5%) | 172.1 (90.9) | 0 | | |
| **Nadir CD4 T-cell count (cells/µl; *mean (SD)*)** | 178.1 (146.0) | 1 (0.6%) | 187.8 (133.1) | 1 (1.7%) | 172.6 (131.7) | 0 |
| **Current CD4 T-cell count (cells/µl; *mean (SD)*)** | 543.3 (265.6) | 2 (1.1%) | 546.2 (261.8) | 1 (1.7%) | 580.5 (331.5) | 0 |
| **AIDS status (*% AIDS*)** | 66.7% | 0 | 59.6% | 0 | 61.4% | 0 |
| **Plasma HIV RNA** | | 1 (0.6%) | | 0 | | 1 (1.7%) |
| % Detectable | 15.8% | | 19.3% | | 8.9% | |
| % Undetectable | 84.2% | | 80.7% | | 91.1% | |
| **Most common ARTs *(N, (%)*)** | | 1 (0.6%) | | 0 | | 3 (5.3%) |
| Tenofovir (TDF)) | 139 (78.5%) | | 41 (71.9%) | | 36 (63.2%) | |
| Emtricitabine (FTC) | 117 (66.1%) | | 40 (70.2%) | | 36 (63.2%) | |
| Ritonavir (RTV) | 101 (57.1%) | | 32 (56.1%) | | 28 (49.1%) | |
| **Changes in ARV Regimen (*%)*** | N/A | | N/A | | 29.8% | 3 (5.3%) |
| **# ARV Medications (*mean (SD)*)** | 3.4 (0.9) | 0 | 3.7 (1.2) | 0 | 3.6 (1.2) | 0 |
| **ARV Pill Burden (*% High*)** [a] | 41.2% | | 63.2% | | 56.1% | 0 |
| **# Non-ARV Medications (*mean (SD)*)** | 4.3 (4.2) | 0 | 4.8 (3.9) | 0 | | |
| **Non-ARV Pill Burden (*% High*)** [a] | 48.6% | | 57.9% | | | |
| **# All Medications (*mean (SD)*)** | 7.7 (4.4) | 0 | 8.5 (4.2) | 0 | | |
| **Total Med Burden (*% High, ARV + non-ARV*)** [a] | 42.9% | | 54.4% | | | |

***Notes.*** [a]Based on a sample-based median split, using the original sample (i.e., N=177) for ease of comparison. Median for ARV medications = 3; median for Non-ARV medications = 3; median for all medications = 7. Participants with number of prescribed medications greater than the median were considered to have "high" pill burden for each category. ARV: Antiretroviral. FTC: emtricitabine. RTV: ritonavir. TDF: tenofovir.

**Table 8**. Experimental characteristics of the longitudinal sample at baseline and at follow-up.

| | ***Baseline*** | | | | ***Follow-up*** | |
|---|---|---|---|---|---|---|
| ***Characteristics*** | ***Full Sample* (N=177)*** | ***# Missing (%)*** | ***Long. Sample* (N=57)*** | ***# Missing (%)*** | ***Long. Sample* (N=57)*** | ***# Missing (%)*** |
| **Adherence** | | | | | | |
| cART Adherence (BERMA MMES)[a] | 77.7 (13.4) | 1 (0.6%) | 76.3 (13.1) | 0 | 75.6 (13.3) | 0 |
| **Memory** | | | | | | |
| Retrospective Memory (CVLT-II)[a] | 10.1 (3.9) | 1 (0.6%) | 9.9 (3.3) | 0 | 9.5 (3.7) | 2 (3.5%) |
| Retrospective Memory (LM II)[a] | 24.7 (9.0) | 0 | 26.0 (7.1) | 0 | 24.0 (7.8) | 1 (1.7%) |
| Prospective Memory (MIST-15)[a] | 5 (1.8) | 0 | 4.2 (1.7) | 0 | 3.8 (1.5) | 0 |
| Prospective Memory (MIST-24) [a] | 0.6 (0.8) | 0 | 0.5 (0.7) | 0 | 0.4 (0.7) | 2 (3.5%) |
| **Fatigue (POMS-FI)[a]** | 8.2 (6.7) | 0 | 8.1 (6.6) | 0 | 8.6 (6.7) | 0 |
| **Compensatory Strategy Use Number (PMMQ, %)[c]** | 42.3% (23.5%) | 77 (43.5%) | 43.6% (24.2%) | 0 | 45.2% (26.2%) | 1 (1.7%) |

***Notes.****Presented as [mean (SD)]. [a]Presented as raw scores. [b]Calculated by 1 – (#pills skipped per day/#pills prescribed) averaged over four days and multiplied by 100. [c]Percent of total number of strategies. Data are presented as means and standard deviations or 95% confidence intervals except where indicated. BERMA MMES: Beliefs Related to cART Adherence, Medication Management Efficiency Scale. CVLT-II: California Verbal Learning Test – Second edition delayed free recall score. LM II: Logical Memory delayed free recall score from the Wechsler Memory Scale III. MIST-15: Memory for Intentions Screening Test, long delay trial. MIST-24: Memory for Intentions Screening Test, 24-hour trial. PMMQ: Prospective Memory for Medications Questionnaire. POMS-FI: The Profile of Mood States, Fatigue-Inertia subscale.

**Table 9**. Pattern of missing data for the longitudinal sample.

| Count | # Columns missing | Current Substance Use T2 | Nadir CD4 T1 | Current CD4 T1 | Plasma HIV RNA T2 | Current cART Regimen T2 | ACTG T1 | ACTG T2 | PMMQ # T1 | MIST-24 HR T2 | LM II T2 | CVLT-II T2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 2 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 3 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Total:** | **20** | **3** | **1** | **1** | **1** | **3** | **2** | **3** | **1** | **2** | **1** | **2** |

***Note.*** Light gray indicates 1-2 repeats of missing variable patterns. ACTG: NIAID AIDS Clinical Trials Group Adherence to Anti-HIV Medications (4 days). GAD: generalized anxiety disorder (current or lifetime). CVLT-II: California Verbal Learning Test – II. LM II: Logical Memory delayed free recall score from the Wechsler Memory Scale III. MIST-24: Memory for Intentions Screening Test, 24-hour trial. PMMQ #: compensatory strategy use number from the Prospective Memory for Medications Questionnaire. T1: time 1. T2: time 2.

**Table 10**. Unstandardized estimates, covariances, and means for the Aim 1 final model.

| | | | Sample-based | | | | Bootstrapped | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Unstandardized Regression Weights** | | | **Estimate** | **S.E.** | **C.R.** | **P** | **SE** | **SE-SE** | **Mean** | **Bias** | **SE-Bias** | **P** |
| adh | <--- | fat | -0.426 | 0.143 | -2.98 | 0.003 | 0.142 | 0.007 | -0.406 | 0.02 | 0.01 | 0.0027 |
| adh | <--- | pml | 10.575 | 4.17 | 2.536 | 0.011 | 4.546 | 0.227 | 11.332 | 0.757 | 0.321 | 0.02001 |
| adh | <--- | csu | -0.168 | 0.058 | -2.917 | 0.004 | 0.065 | 0.003 | -0.168 | 0 | 0.005 | 0.00975 |
| m | <--- | adh | 1 | | | | 0 | 0 | 1 | 0 | 0 | |
| b | <--- | adh | 1.624 | 0.491 | 3.305 | <.001 | 0.687 | 0.034 | 1.821 | 0.197 | 0.049 | 0.01808 |
| c | <--- | rml | 1 | | | | 0 | 0 | 1 | 0 | 0 | |
| l | <--- | rml | 2.422 | 0.42 | 5.767 | <.001 | 0.396 | 0.02 | 2.415 | -0.006 | 0.028 | <.001 |
| 24 | <--- | pml | 1 | | | | 0 | 0 | 1 | 0 | 0 | |
| 15 | <--- | pml | 3.235 | 0.836 | 3.869 | <.001 | 1.154 | 0.058 | 3.488 | 0.253 | 0.082 | 0.00506 |
| **Covariances** | | | **Estimate** | **S.E.** | **C.R.** | **P** | **SE** | **SE-SE** | **Mean** | **Bias** | **SE-Bias** | **P** |
| pml | <--> | rml | 0.744 | 0.205 | 3.622 | <.001 | 0.206 | 0.01 | 0.732 | -0.013 | 0.015 | 0.0003 |
| fat | <--> | csu | 30.949 | 8.275 | 3.74 | <.001 | 7.477 | 0.374 | 30.075 | -0.874 | 0.529 | <.001 |
| **Unstandardized Means** | | | **Estimate** | **S.E.** | **C.R.** | **P** | **SE** | **SE-SE** | **Mean** | **Bias** | **SE-Bias** | |
| fat | | | 8.249 | 0.505 | 16.35 | <.001 | 0.51 | 0.025 | 8.196 | -0.053 | 0.036 | |
| csu | | | 28.64 | 1.186 | 24.146 | <.001 | 1.12 | 0.056 | 28.642 | 0.002 | 0.079 | |

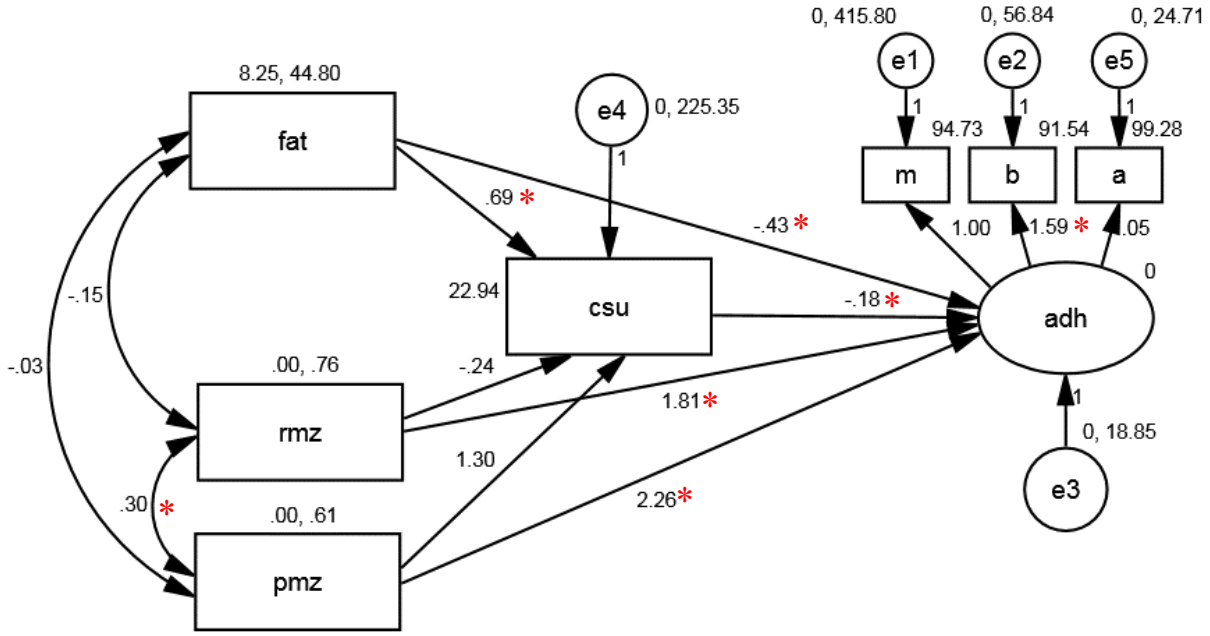
***Note.*** adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: prospective memory latent variable comprised of the Memory for Intentions Screening Test 15-minute (15) and 24-hour (24) delay trials. rml: retrospective memory latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Table 11.** Unstandardized estimates and covariances for the Aim 2 final model.

| | | | Sample-based | | | |
|---|---|---|---|---|---|---|
| **Unstandardized Regression Weights** | | | **Estimate** | **S.E.** | **C.R.** | **P** |
| csu time 1 | <--- | I-csu | 1 | | | |
| csu time 2 | <--- | S-csu | 1 | | | |
| csu time 1 | <--- | S-csu | 0 | | | |
| csu time 2 | <--- | I-csu | 1 | | | |
| bmmes time 2 | <--- | S-bmmes | 1 | | | |
| bmmes time 1 | <--- | I-bmmes | 1 | | | |
| bmmes time 2 | <--- | I-bmmes | 1 | | | |
| bmmes time 1 | <--- | S-bmmes | 0 | | | |
| fat time 1 | <--- | I-fat | 1 | | | |
| fat time 2 | <--- | S-fat | 1 | | | |
| fat time 1 | <--- | S-fat | 0 | | | |
| fat time 2 | <--- | I-fat | 1 | | | |
| **Covariances** | | | **Estimate** | **S.E.** | **C.R.** | **P** |
| I-csu | <--> | I-bmmes | -1.546 | 0.434 | -3.557 | <.001 |
| I-bmmes | <--> | I-fat | -45.476 | 11.705 | -3.885 | <.001 |
| S-fat | <--> | S-bmmes | -25.583 | 8.864 | -2.886 | 0.004 |
| S-csu | <--> | S-bmmes | -0.713 | 0.286 | -2.488 | 0.013 |
| S-fat | <--> | S-csu | 0.318 | 0.15 | 2.119 | 0.034 |
| I-csu | <--> | I-fat | 0.479 | 0.197 | 2.426 | 0.015 |

***Note*** . bmmes: Medication Management Efficiency Scale from the Beliefs Related to cART Adherence, Medication Management Efficiency Scale. csu: compensatory strategy use number from the Prospective Memory for Medications Questionnaire. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. I-intercept. S-slope.

**Figure 1**. The omnibus Aim 1 model.




**Model Fit**

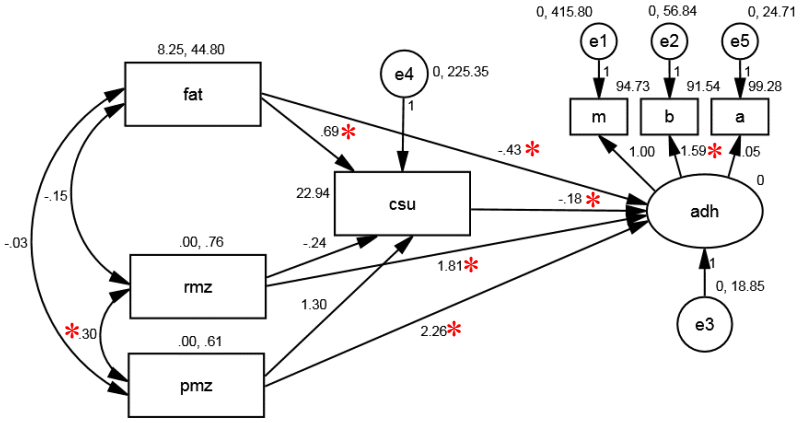
| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 9.846 | 8 | 0.276 | 1.231 | 0.941 | **0.967** | **0.987** | **0.036** | 63.85 |

***Note*. Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit.

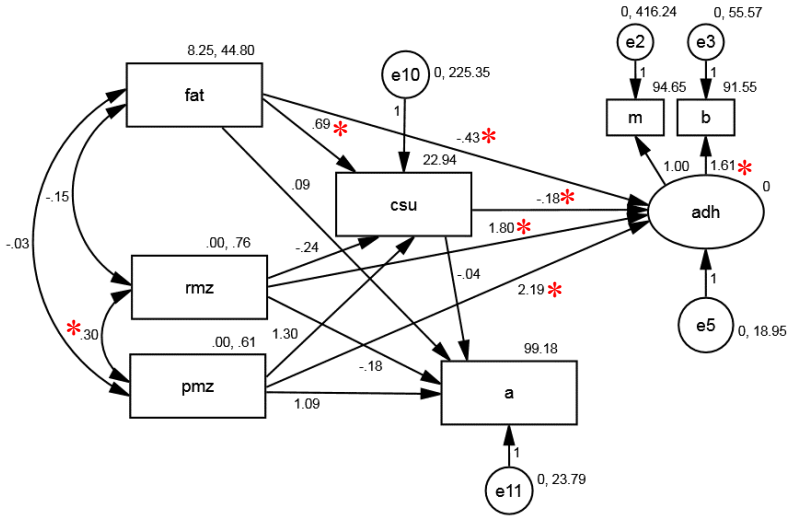
**Fig.1.** Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the AIDS Clinical Trials Group Adherence to Anti-HIV Medications (ACTG) questionnaire (ACTG; a), the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (BERMA MMES; b), and the medication event monitoring system (MEMS; m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire (PMMQ). e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale (POMS-FI). pmz: prospective memory (PM) composite score. rmz: retrospective memory (RM) composite score.

**Figure 2**. Determination of adherence variable.

**A.**




**B.**




**C.**

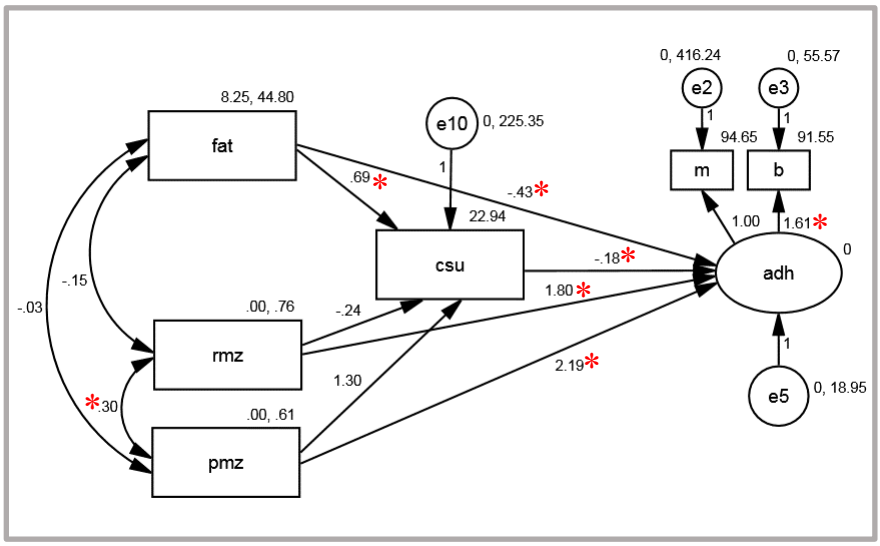


**Figure 2**. Determination of adherence variable (continued).

**Model Fit**

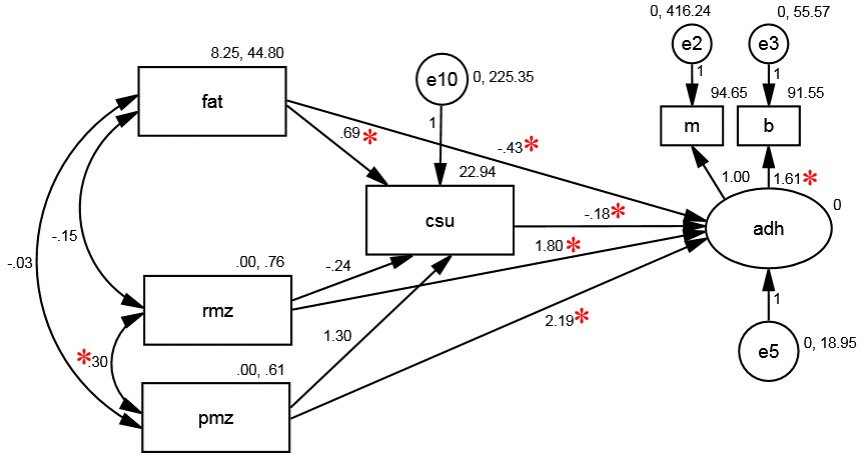
| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **2A** | 9.846 | 8 | 0.276 | 1.231 | 0.941 | **0.967** | **0.987** | **0.036** | 63.85 |
| **2B** | 2.263 | 5 | 0.812 | 0.453 | **0.987** | **1.076** | **1.000** | **0.000** | 62.26 |
| **2C** | 1.965 | 3 | 0.580 | 0.655 | **0.988** | **1.035** | **1.000** | **0.000** | 49.97 |

***Note.*** Bold denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Model C is outlined to emphasize best conceptual agreement with acceptable indices of fit.

**Fig.2. 2A:** ACTG included as a factor in the adherence latent variable. **2B**: ACTG included as an independent endogenous variable. **2C**: ACTG removed from the model. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. a: AIDS Clinical Trials Group Adherence to Anti-HIV Medications (ACTG). adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire (PMMQ). e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale (POMS-FI). pmz: prospective memory composite score. rmz: retrospective memory composite score.

**Figure 3**. Determination of memory variable.

**A.**




**B.**

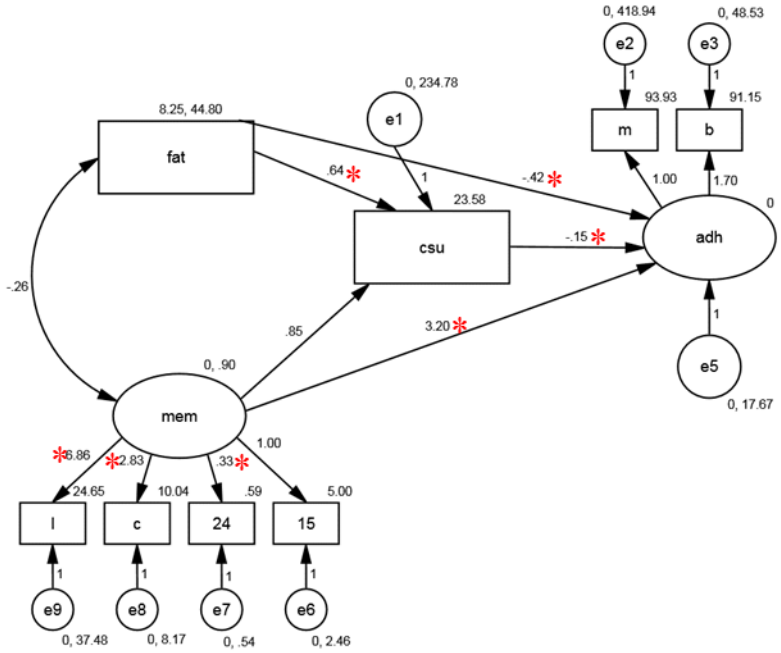
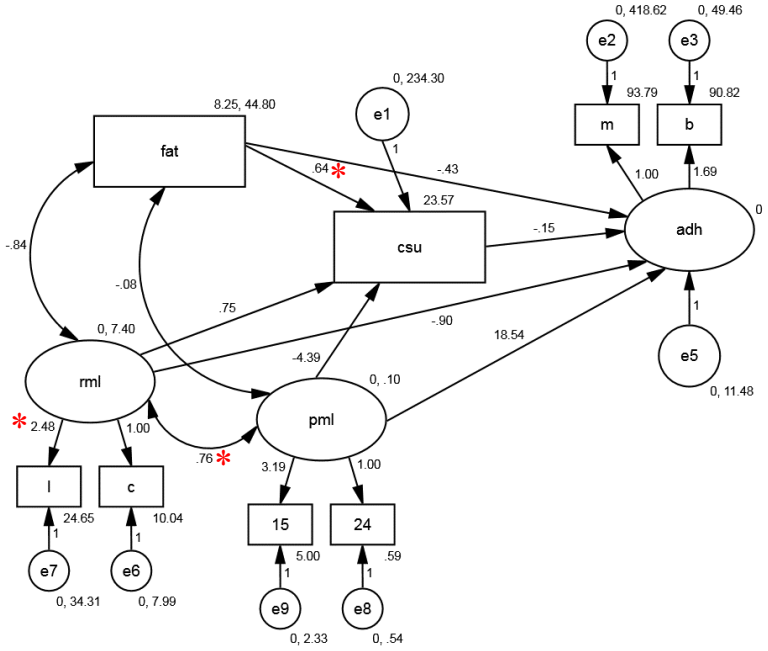


**Figure 3**. Determination of memory variable (continued).

**C.**




**D.**

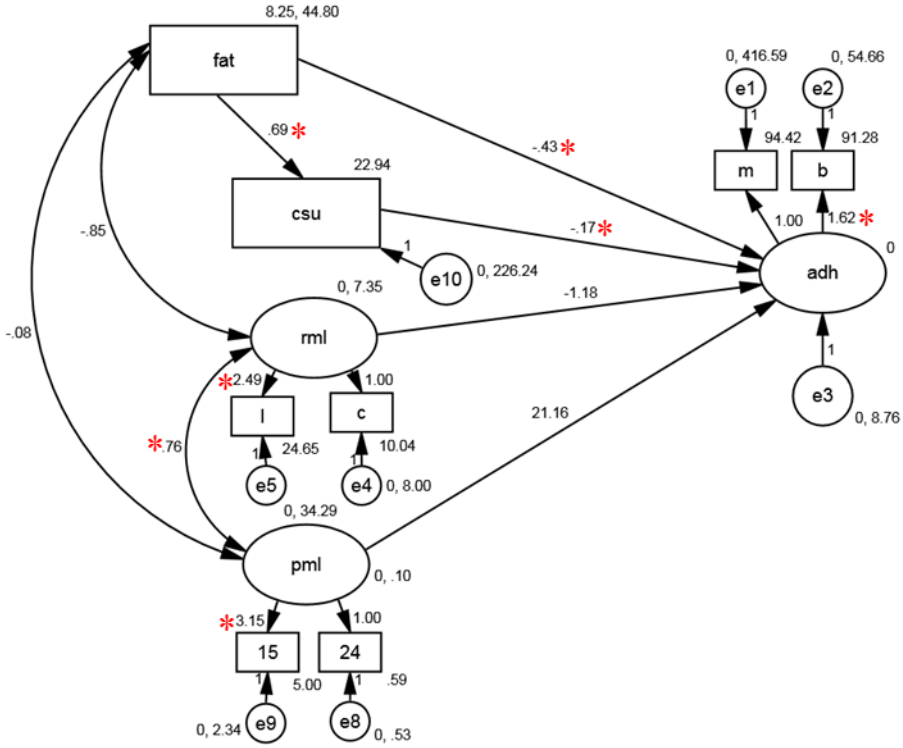
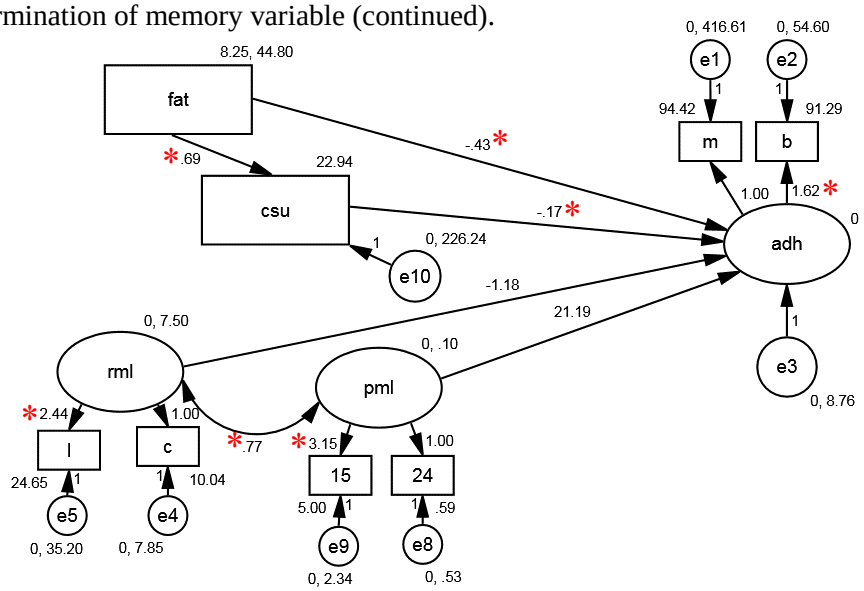
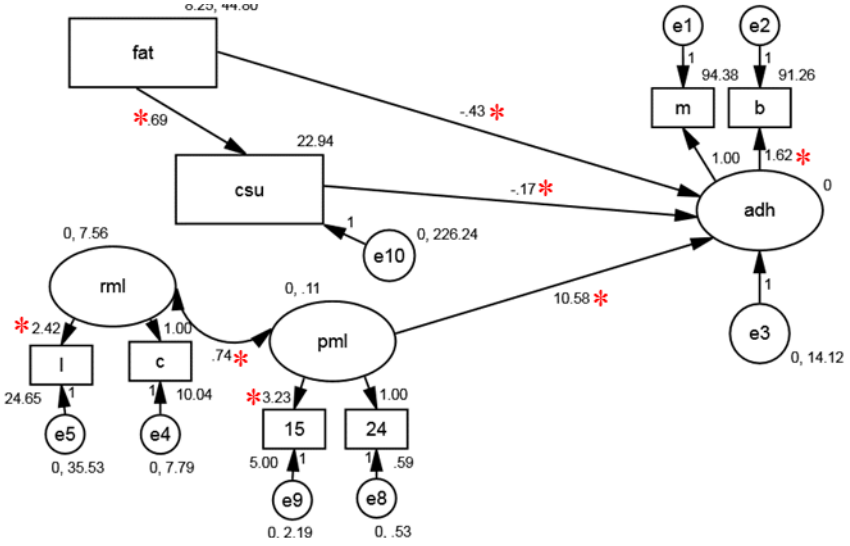


**Figure 3.** Determination of memory variable (continued).

**E.**




**F.**




**G.**

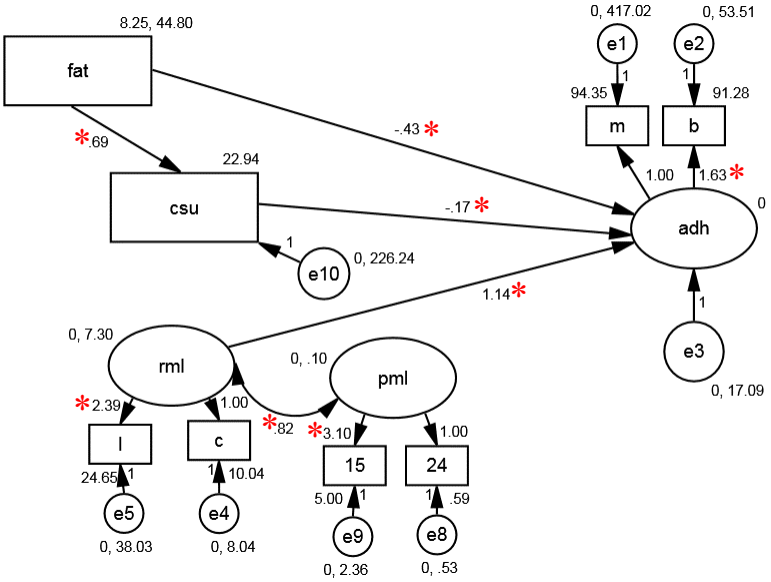
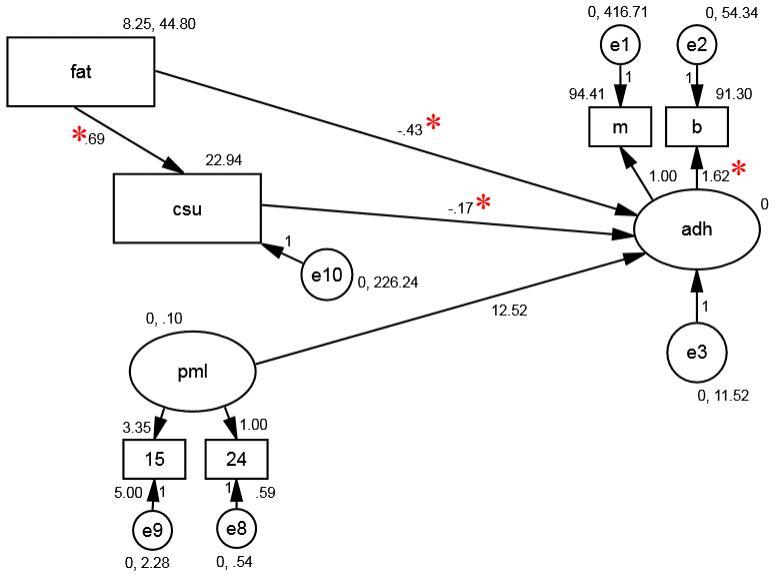


**Figure 3**. Determination of memory variable (continued).

**H.**




**Model Fit**

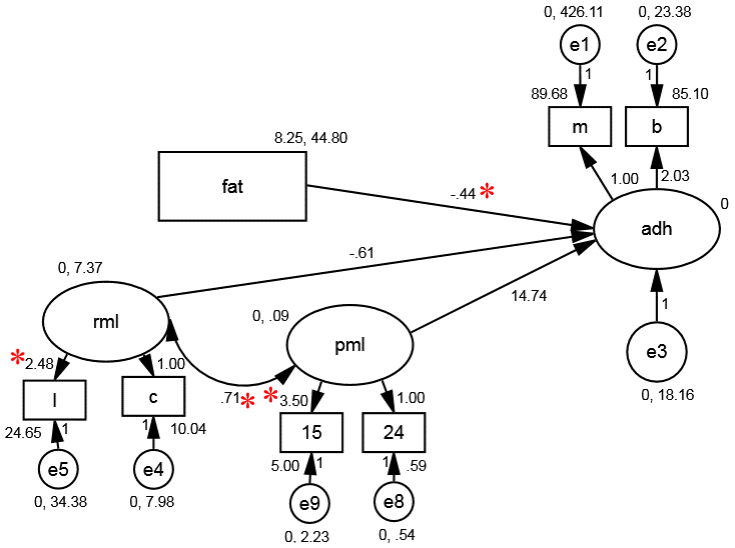
| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **3A** | 1.965 | 3 | 0.580 | 0.655 | **0.988** | **1.035** | **1.000** | **0.000** | 49.97 |
| **3B** | 20.680 | 16 | 0.191 | 1.292 | 0.914 | **0.962** | **0.978** | **0.041** | 76.68 |
| **3C** | 16.871 | 12 | 0.155 | 1.406 | 0.930 | 0.947 | **0.977** | **0.048** | 80.87 |
| **3D** | 16.833 | 14 | 0.265 | 1.202 | 0.932 | **0.974** | **0.987** | **0.034** | 76.83 |
| **3E** | 17.089 | 16 | 0.380 | 1.068 | 0.931 | **0.991** | **0.995** | **0.020** | 73.09 |
| **3F** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **3G** | 21.341 | 17 | 0.211 | 1.255 | 0.913 | **0.967** | **0.980** | **0.038** | 75.341 |
| **3H** | 11.217 | 7 | 0.129 | 1.602 | 0.918 | 0.925 | **0.965** | **0.059** | 51.217 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Model F is outlined to emphasize best conceptual agreement with acceptable indices of fit.

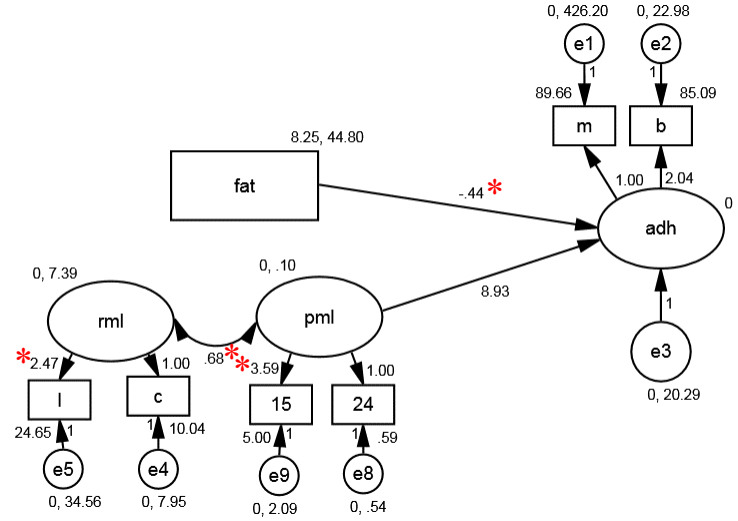
**Fig.3. 3A:** Memory as two composite scores. **3B**: Memory as an aggregate latent variable. **3C**: Memory as two latent variables. **3D**: Removal of nonsignificant estimates between memory and CSU. **3E**: Removal of nonsignificant covariances between memory and fatigue. **3F**: Removal of nonsignificant estimate between RM and adherence. **3G** Removal of nonsignificant estimate between PM and adherence. **3H**: Removal of RM from the model. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: prospective memory latent variable comprised of the Memory for Intentions Screening Test (MIST) 15-minute (15) and 24-hour (24) delay trials. pmz: prospective memory composite score. rml: retrospective memory latent variable comprised of the California Verbal Learning Test – Second edition delayed free recall score (c) and the Logical Memory delayed free recall score (l) from the Wechsler Memory Scale III. rmz: retrospective memory composite score.

**Figure 4**. Assessing direct effects of fatigue and memory on adherence.

**A.**




**B.**




**C.**

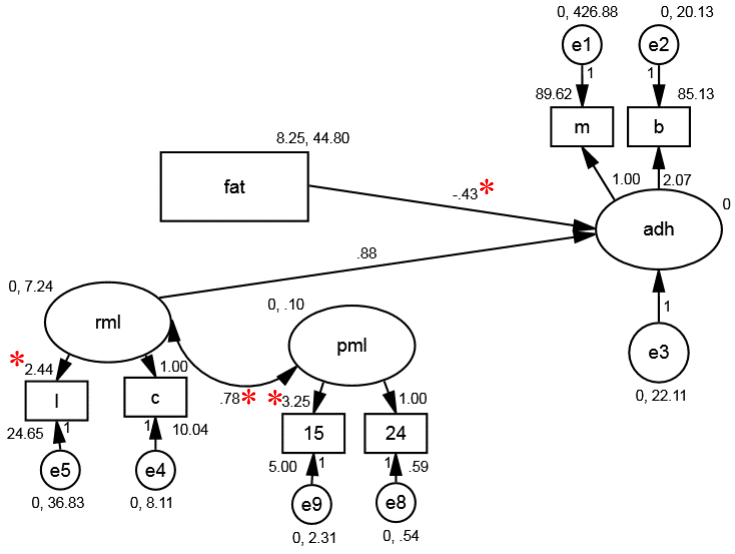


**Figure 4**. Assessing direct effects of fatigue and memory on adherence (continued).

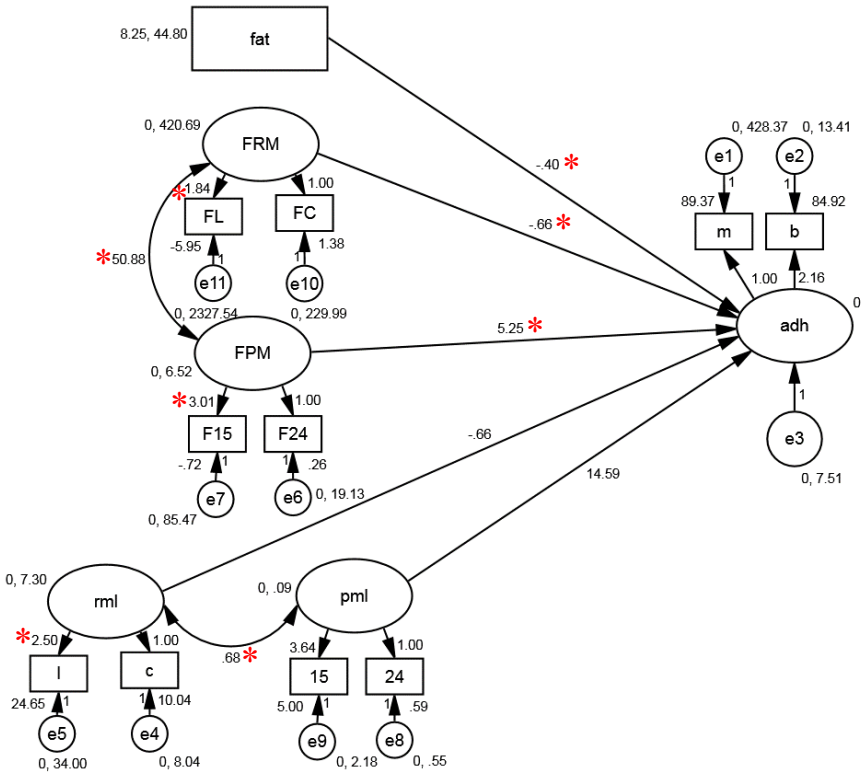
| | Model Fit | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | CMIN | DF | ***p*** | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
| **4A** | 7.992 | 11 | 0.714 | 0.727 | **0.959** | **1.033** | **1.000** | **0.000** | 55.992 |
| **4B** | 8.288 | 12 | 0.762 | 0.691 | **0.957** | **1.037** | **1.000** | **0.000** | 54.288 |
| **4C** | 11.63 | 12 | 0.476 | 0.969 | 0.94 | **1.004** | **1.000** | **0.000** | 57.63 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit.

**Fig.4. 4A:** Default model. **4B**: Removal of nonsignificant estimate between RM and adherence. **4C:** Removal of nonsignificant estimate between PM and adherence. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: prospective memory latent variable comprised of the Memory for Intentions Screening Test 15-minute (15) and 24-hour (24) delay trials. rml: retrospective memory latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 5**. Assessing interactive effects between fatigue and memory on adherence.

**A.**




**B.**

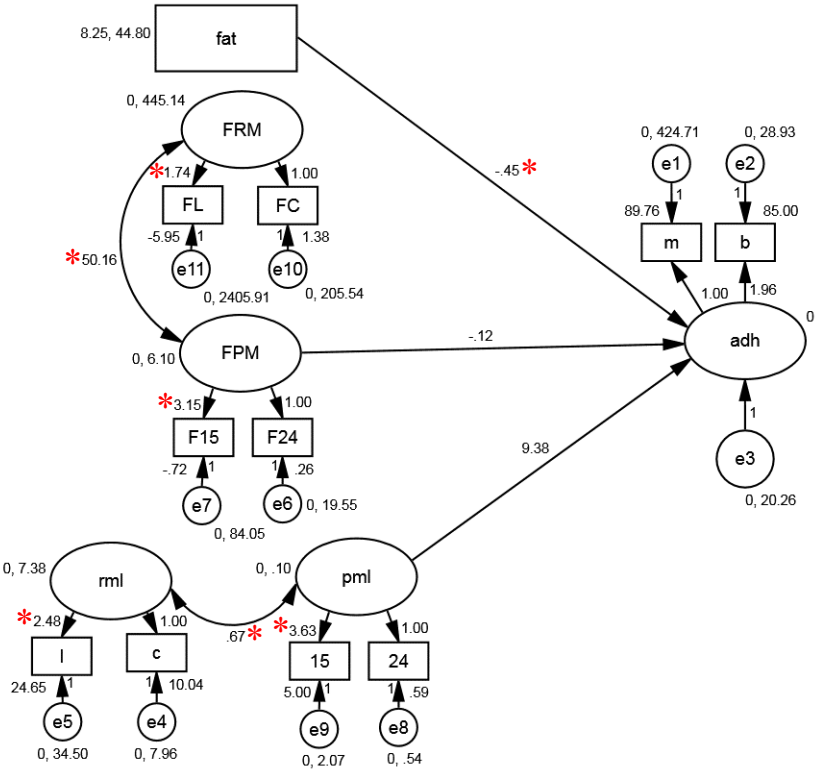
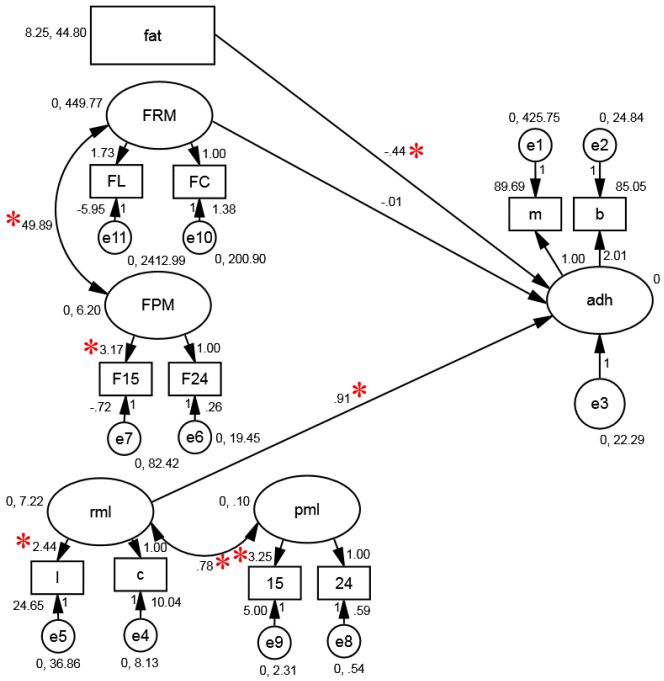


**Figure 5**. Assessing interactive effects between fatigue and memory on adherence (continued).

**C.**




**Model Fit**

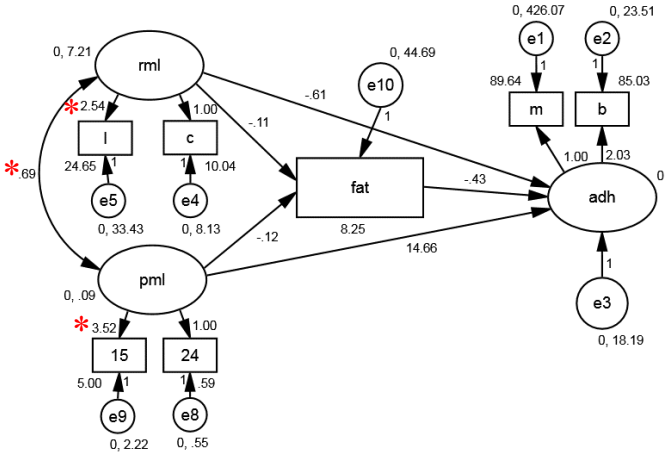
| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **5A** | 62.40 | 38 | 0.008 | 1.642 | 0.842 | 0.896 | 0.928 | 0.060 | 140.40 |
| **5B** | 65.21 | 40 | 0.007 | 1.630 | 0.835 | 0.898 | 0.926 | 0.060 | 139.21 |
| **5C** | 68.66 | 40 | 0.003 | 1.717 | 0.826 | 0.884 | 0.916 | 0.064 | 142.66 |

***Note.*** Gray denotes significant chi-square results, one indicator of poor model fit.

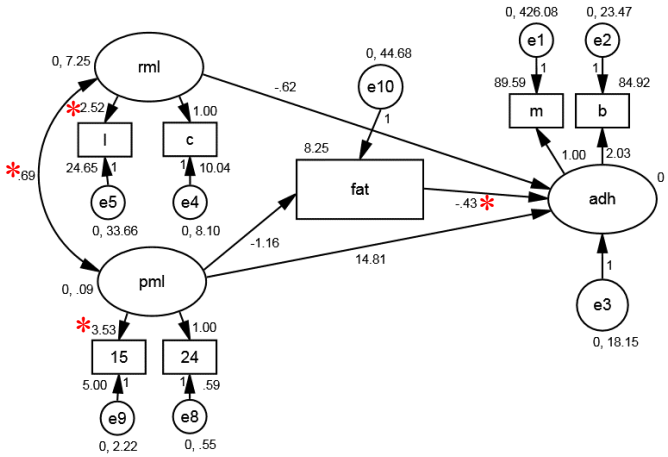
**Fig.5. 5A:** Default model. **5B**: Removal of nonsignificant estimates between RM/FRM and adherence. **5C:** Removal of nonsignificant estimates between PM/FPM and adherence. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. FPM: latent variable of the interaction between fatigue and prospective memory comprised of product constants for fatigue and the Memory for Intentions Screening Test 15-minute (F15) and 24-hour (F24) delay trials. FRM: latent variable of the interaction between fatigue and retrospective memory comprised of product constants for fatigue and the California Verbal Learning Test – II (FC) and Logical Memory (FL) from the Wechsler Memory Scale III. pml: prospective memory latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: retrospective memory latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 6**. Assessing mediating effects of fatigue on memory and adherence.

**A.**




**B.**




**C.**

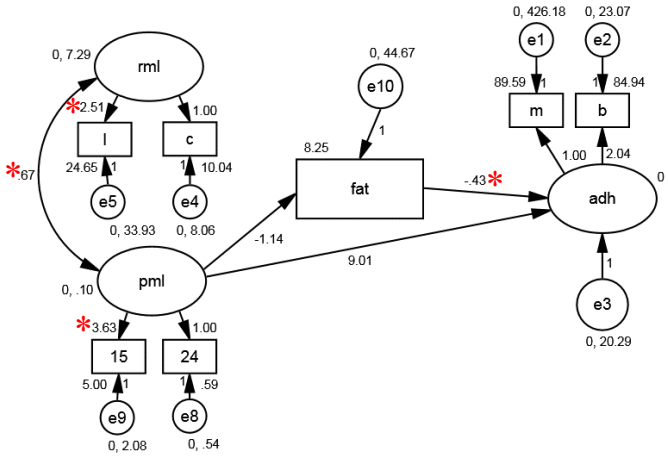
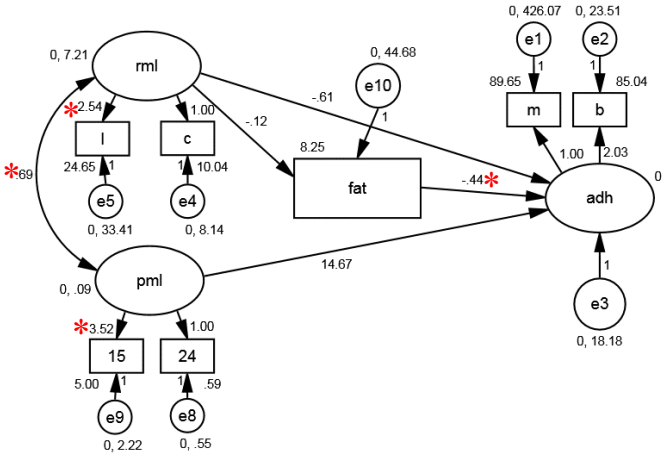
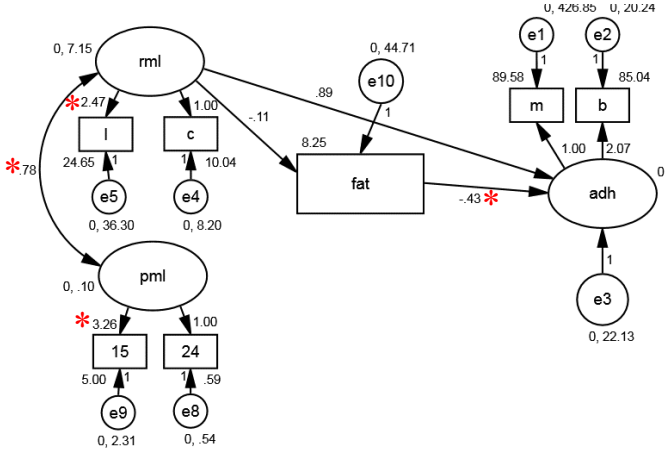


**Figure 6**. Assessing mediating effects of fatigue on memory and adherence (continued).

**D.**




**E.**




**Model Fit**

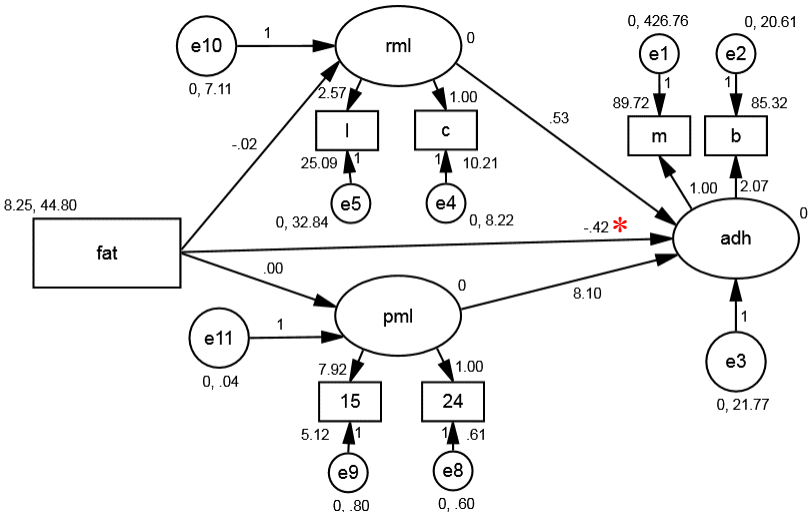
| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **6A** | 7.688 | 9 | 0.566 | 0.854 | **0.961** | **1.018** | **1.000** | **0.000** | 59.688 |
| **6B** | 7.701 | 10 | 0.658 | 0.658 | **0.961** | **1.028** | **1.000** | **0.000** | 57.701 |
| **6C** | 7.996 | 11 | 0.714 | 0.727 | **0.959** | **1.016** | **1.000** | **0.000** | 55.996 |
| **6D** | 7.688 | 10 | 0.659 | 0.769 | **0.961** | **1.012** | **1.000** | **0.000** | 57.688 |
| **6E** | 11.382 | 11 | 0.412 | 1.035 | 0.942 | **0.996** | **0.998** | **0.014** | 59.382 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit.

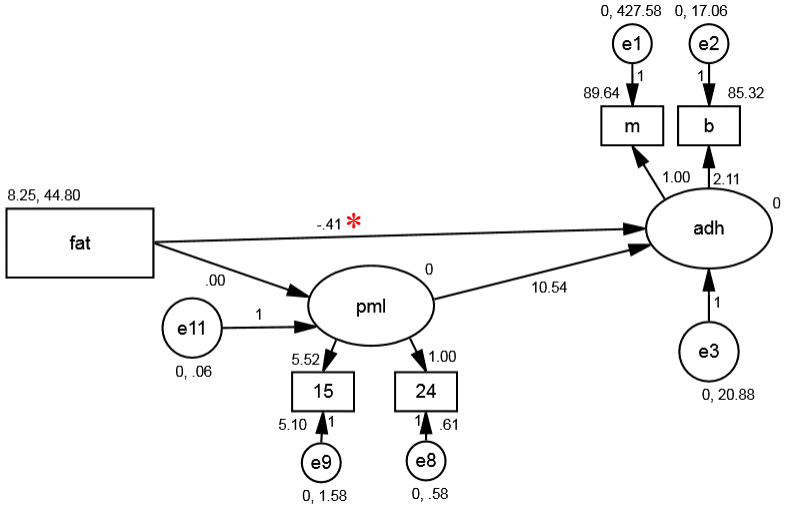
**Fig.6. 6A:** Default model. **6B**: Removal of nonsignificant estimate between RM and fatigue. **6C:** Removal of nonsignificant estimate between RM and adherence. **6D**: Removal of nonsignificant estimate between PM and fatigue. **6E:** Removal of nonsignificant estimate between PM and adherence. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: prospective memory latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: retrospective memory latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 7**. Assessing mediating effects of memory on fatigue and adherence.

**A.**




**B.**




**C.**

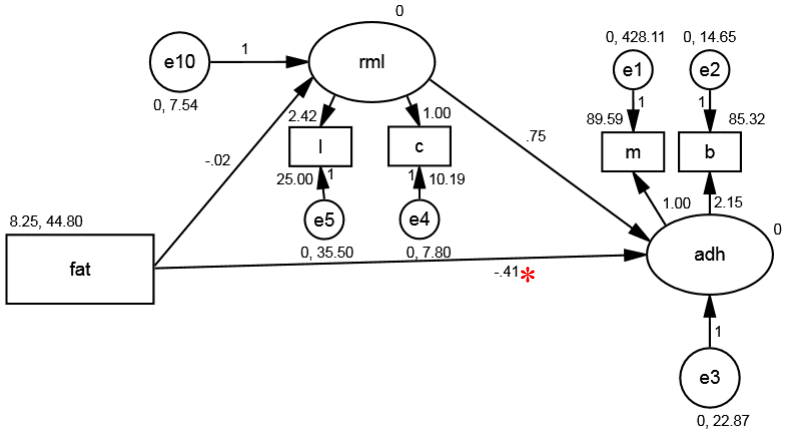


**Figure 7**. Assessing mediating effects of memory on fatigue and adherence (continued).

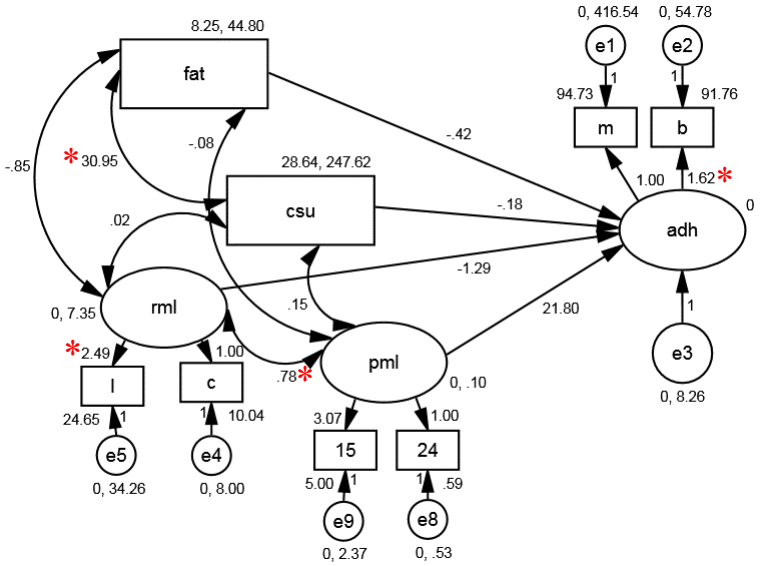
| | Model Fit | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | CMIN | DF | ***p*** | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
| **7A** | 46.434 | 10 | 0.000 | 4.643 | 0.762 | 0.56 | 0.791 | 0.144 | 96.434 |
| **7B** | 1.392 | 3 | 0.707 | 0.464 | **0.984** | **1.070** | **1.000** | **0.000** | 35.392 |
| **7C** | 4.673 | 3 | 0.197 | 1.558 | **0.965** | **0.955** | **0.986** | **0.056** | 38.673 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Gray denotes significant chi-square results, one indicator of poor model fit.

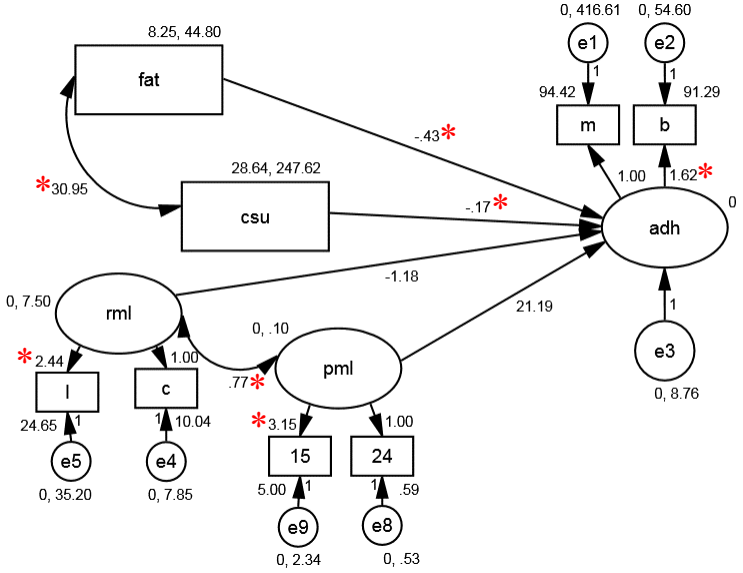
**Fig.7. 7A:** Default model. **7B**: Removal of RM from the model. **7C:** Removal of PM from the model. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 8.** Assessing direct effects of fatigue, memory, and strategy use on adherence.

**A.**




**B.**




**C.**

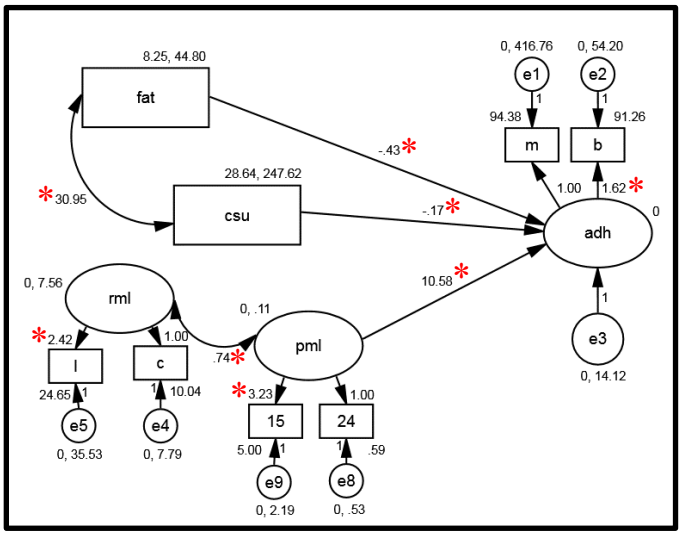
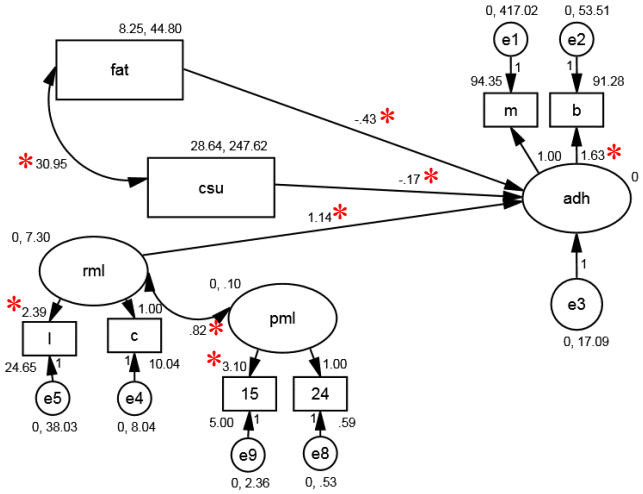


**Figure 8**. Assessing direct effects of fatigue, memory, and strategy use on adherence (continued).

**D.**




**Model Fit**

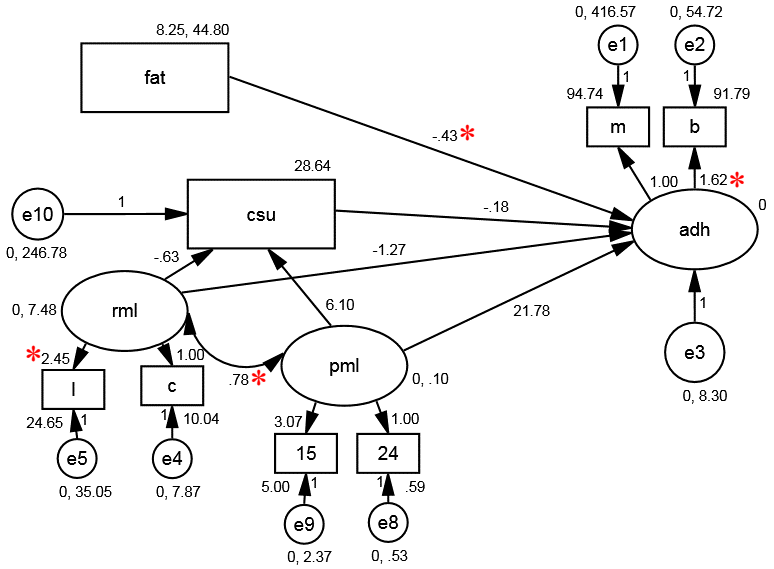
| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **8A** | 16.731 | 12 | 0.160 | 1.394 | 0.932 | 0.949 | **0.978** | **0.047** | 80.731 |
| **8B** | 17.089 | 16 | 0.380 | 1.068 | 0.931 | **0.991** | **0.995** | **0.020** | 73.089 |
| **8C** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **8D** | 21.341 | 17 | 0.211 | 1.255 | 0.913 | **0.967** | **0.980** | **0.038** | 75.341 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Model 8C is outlined to emphasize best model fit.

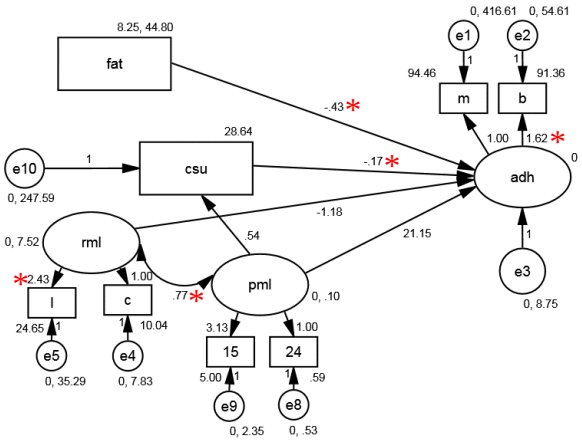
**Fig.8. 8A:** Default model. **8B**: Removal of nonsignificant covariances. **8C:** Removal of nonsignificant estimate between RM and adherence. **8D:** Removal of nonsignificant estimate between PM and adherence. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 9.** Assessing mediating effects of strategy use on memory and adherence.

**A.**




**B.**




**C.**

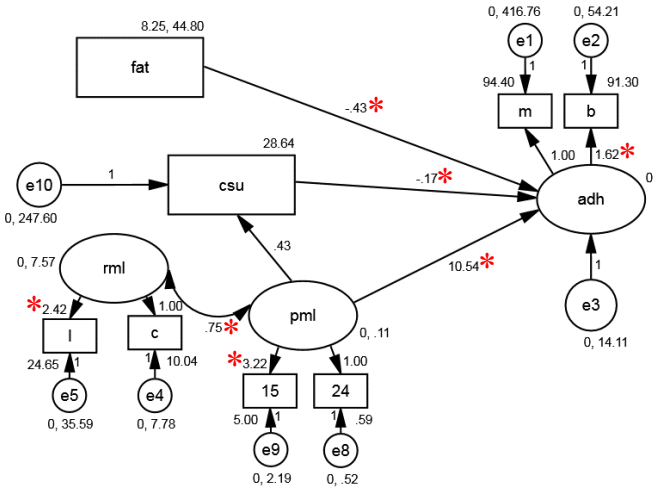
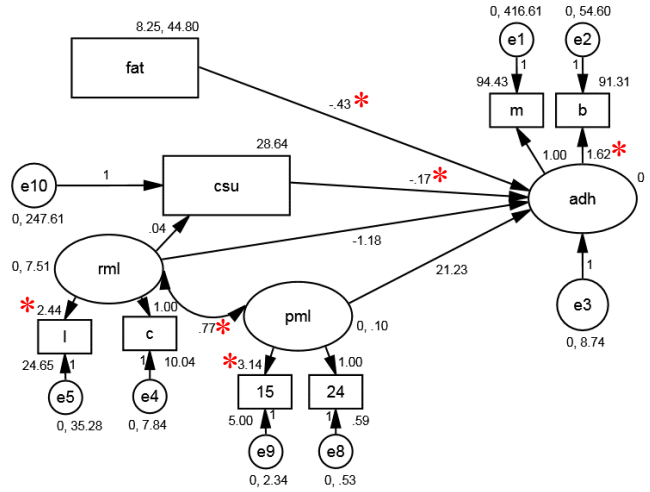


**Figure 9.** Assessing mediating effects of strategy use on memory and adherence **(**continued).

**D.**




**E.**

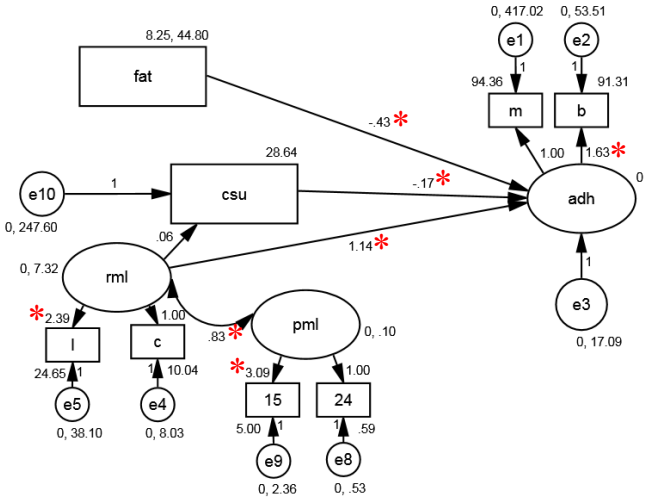


**Figure 9.** Assessing mediating effects of strategy use on memory and adherence **(**continued).

**Model Fit**

| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **9A** | 32.929 | 15 | 0.005 | 2.195 | 0.866 | 0.847 | 0.918 | 0.082 | 90.929 |
| **9B** | 32.970 | 16 | 0.007 | 2.061 | 0.866 | 0.864 | 0.922 | 0.078 | 88.970 |
| **9C** | 33.480 | 17 | 0.010 | 1.969 | 0.864 | 0.876 | 0.925 | 0.074 | 87.480 |
| **9D** | 32.977 | 16 | 0.007 | 2.061 | 0.866 | 0.864 | 0.922 | 0.078 | 88.977 |
| **9E** | 37.222 | 17 | 0.003 | 2.190 | 0.849 | 0.847 | 0.907 | 0.082 | 91.222 |

***Note.*** Gray denotes significant chi-square results, one indicator of poor model fit.

**Fig.9. 9A:** Default model. **9B**: Removal of nonsignificant estimate between RM and CSU. **9C:** Removal of nonsignificant estimate between RM and adherence. **8D:** Removal of nonsignificant estimate between PM and CSU. **9E**: Removal of nonsignificant estimate between PM and adherence. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 10.** Assessing interactive effects between fatigue and strategy use on adherence.

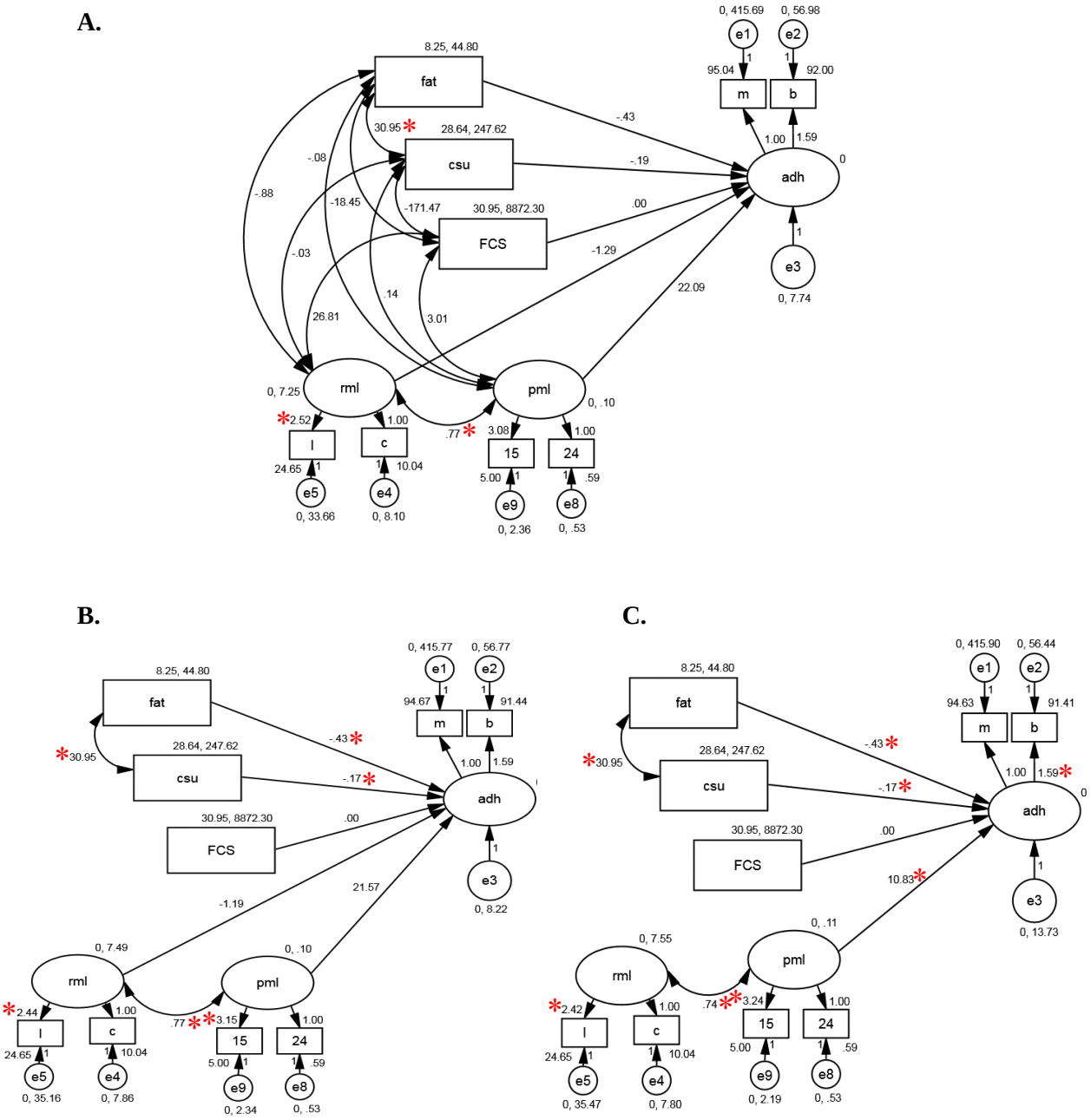
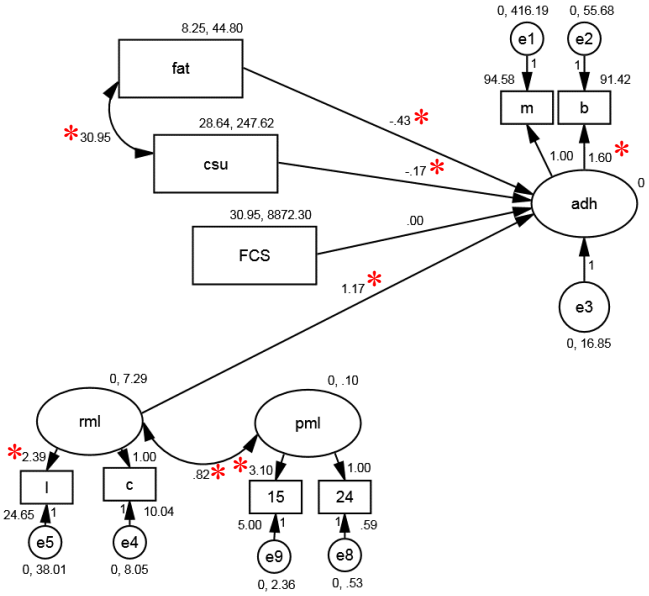


**Figure 10.** Assessing interactive effects between fatigue and strategy use on adherence (continued).

**D.**




**Model Fit**

| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **10A** | 20.330 | 15 | 0.160 | 1.36 | 0.920 | 0.941 | **0.976** | **0.045** | 98.330 |
| **10B** | 24.574 | 23 | 0.373 | 1.068 | 0.903 | **0.989** | **0.993** | **0.020** | 86.574 |
| **10C** | 25.072 | 24 | 0.402 | 1.045 | 0.901 | **0.993** | **0.995** | **0.016** | 85.072 |
| **10D** | 28.841 | 24 | 0.226 | 1.202 | 0.886 | **0.967** | **0.978** | **0.034** | 88.841 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit.

**Fig.10. 10A:** Default model. **10B**: Removal of nonsignificant covariances. **10C:** Removal of nonsignificant estimate between RM and adherence. **10D:** Removal of nonsignificant estimate between PM and adherence. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire (PMMQ). e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale (POMS-FI). FCS: latent variable of the interaction between fatigue and strategy use comprised of product constants for the POMS-FI and the PMMQ. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 11**. Assessing interactive effects between memory and strategy use on adherence.

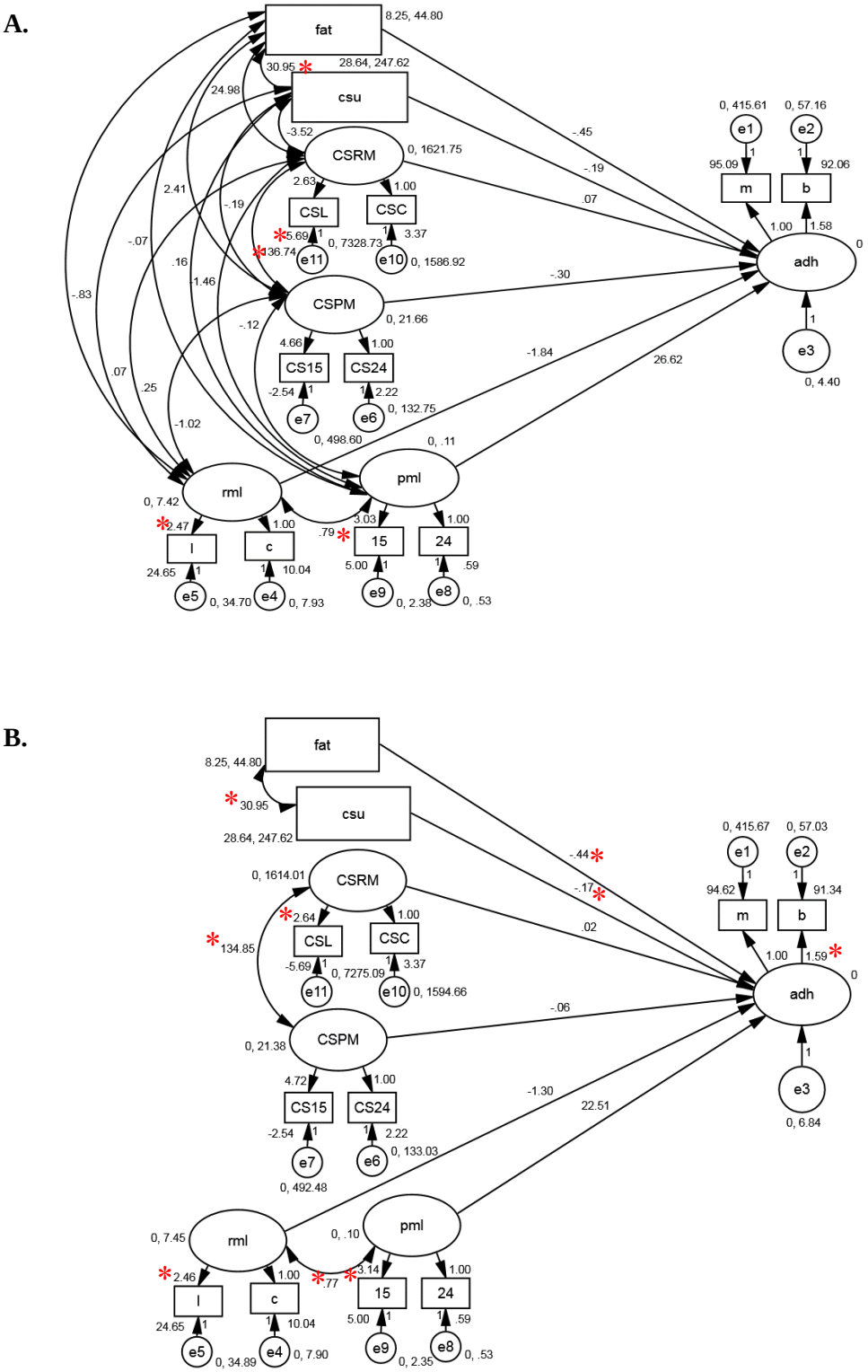
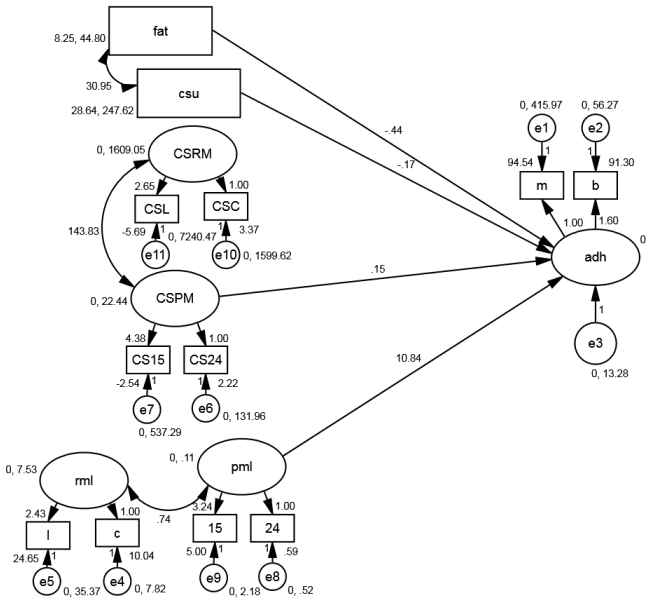


**Figure 11.** Assessing interactive effects between memory and strategy use on adherence (continued).

**C.**




**D.**

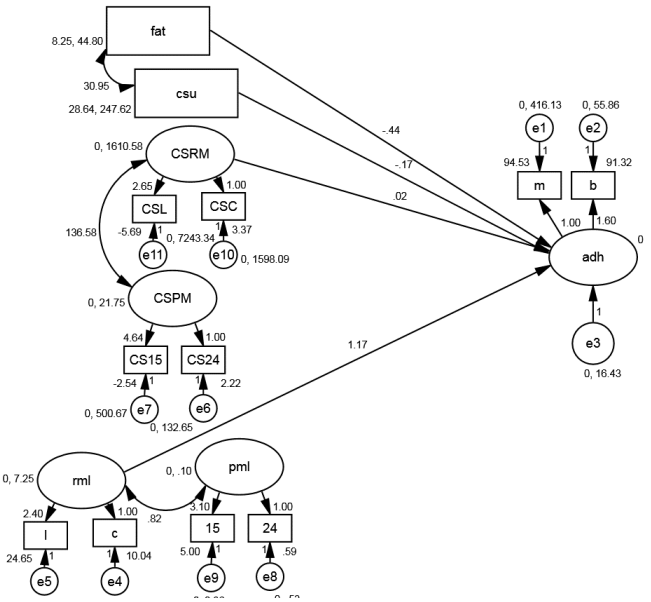
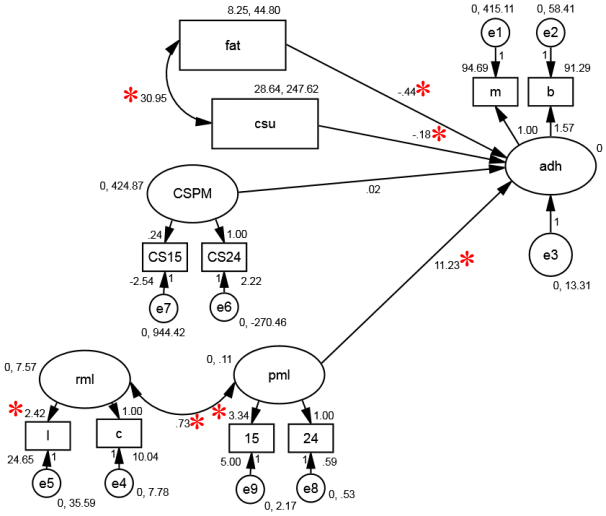


**Figure 11.** Assessing interactive effects between memory and strategy use on adherence (continued).

**E.**




**F.**

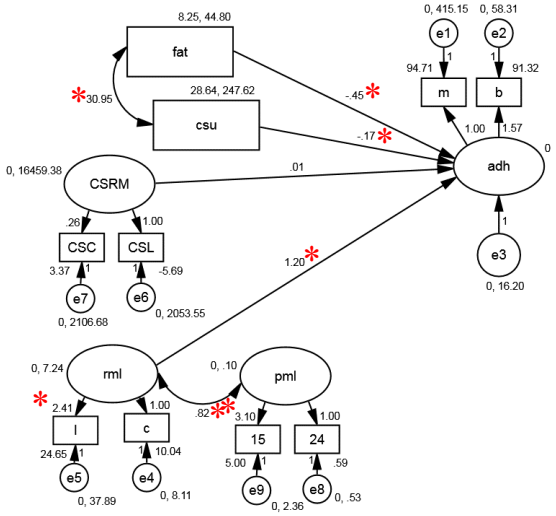


**Figure 11**. Assessing interactive effects between memory and strategy use on adherence (continued).

**Model Fit**

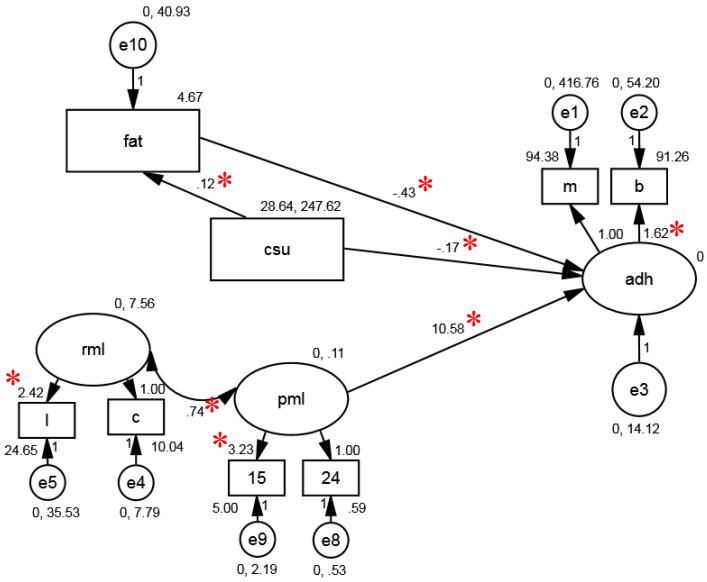
| | CMIN | DF | *p* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **11A** | 37.91 | 35 | 0.338 | 1.083 | 0.902 | **0.983** | **0.991** | **0.022** | 147.910 |
| **11B** | 40.926 | 47 | 0.721 | 0.871 | 0.895 | **1.026** | **1.000** | **0.000** | 126.296 |
| **11C** | No text output- estimated variances of one variable failed to be positive, which interfered with attempt to fit the model by computing a standardized regression weight | | | | | | | | |
| **11D** | No text output- estimated variances of one variable failed to be positive, which interfered with attempt to fit the model by computing a standardized regression weight | | | | | | | | |
| **11E** | 28.719 | 31 | 0.584 | 0.926 | 0.895 | **1.015** | **1.000** | **0.000** | 96.719 |
| **11F** | 31.070 | 31 | 0.463 | 1.002 | 0.903 | **1.000** | **1.000** | **0.004** | 99.070 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit.

**Fig.11. 11A:** Default model. **11B**: Removal of nonsignificant covariates. **11C:** Removal of nonsignificant estimates between RM/CSRM and adherence. **11D:** Removal of nonsignificant estimates between PM/CSPM and adherence. **11E:** Removal of CSRM. **11F:** Removal of CSPM. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). CSPM: latent variable of the interaction between strategy use and prospective memory comprised of product constants for the PMMQ and the Memory for Intentions Screening Test 15-minute (CS15) and 24-hour (CS24) delay trials. CSRM: latent variable of the interaction between strategy use and retrospective memory comprised of product constants for the PMMQ and the California Verbal Learning Test – II (CSC) and Logical Memory (CSL) from the Wechsler Memory Scale III. csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire (PMMQ). e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 12.** Determination of the best-fitting model.

**A.**




**B.**

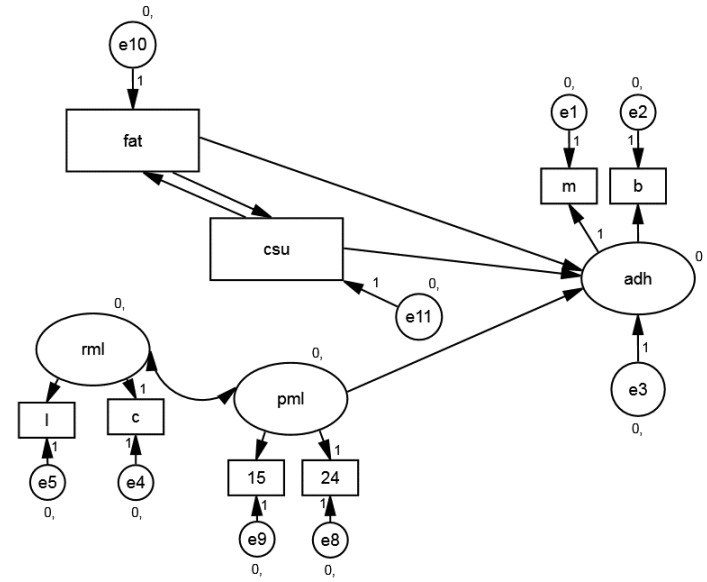


**Figure 12.** Determination of the best-fitting model (continued).

**Model Fit**

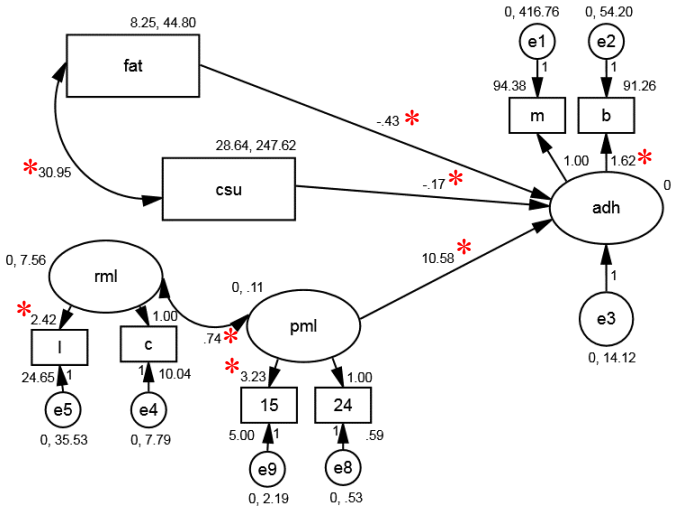
| | CMIN | DF | ***P*** | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **8C** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **3F** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **12A** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **12B** | N/A - the model is not recursive | | | | | | | | |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Model 8C is outlined to emphasize best model fit.

**Fig.12. 12A:** Assessment of mediating effects of strategy use on fatigue and adherence. **12B**: Assessment of the relative effects of fatigue and strategy use on one another. **8C** and **3F** refer to Figures 8 and 3 respectively, as candidates of the best-fitting Aim 1 model. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable comprised of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 13.** Covariate analyses.

**A.**




**B.**

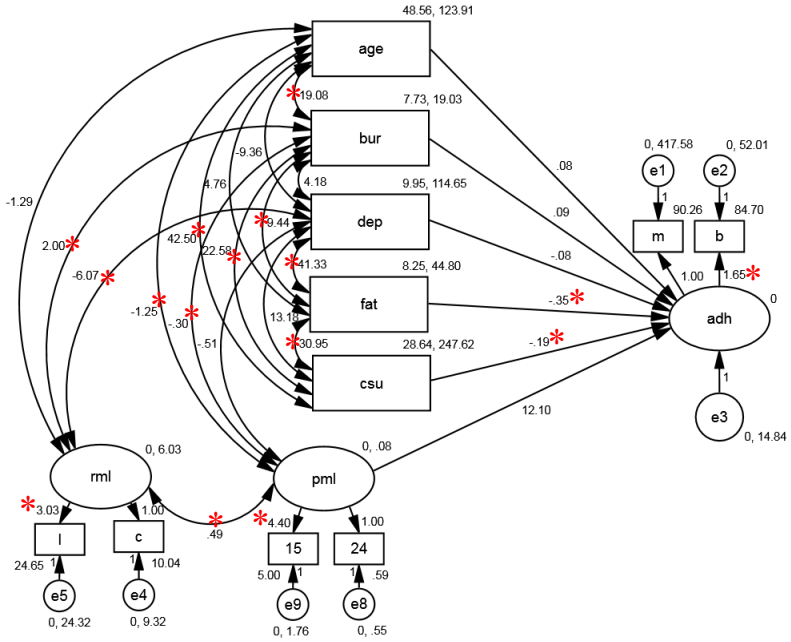
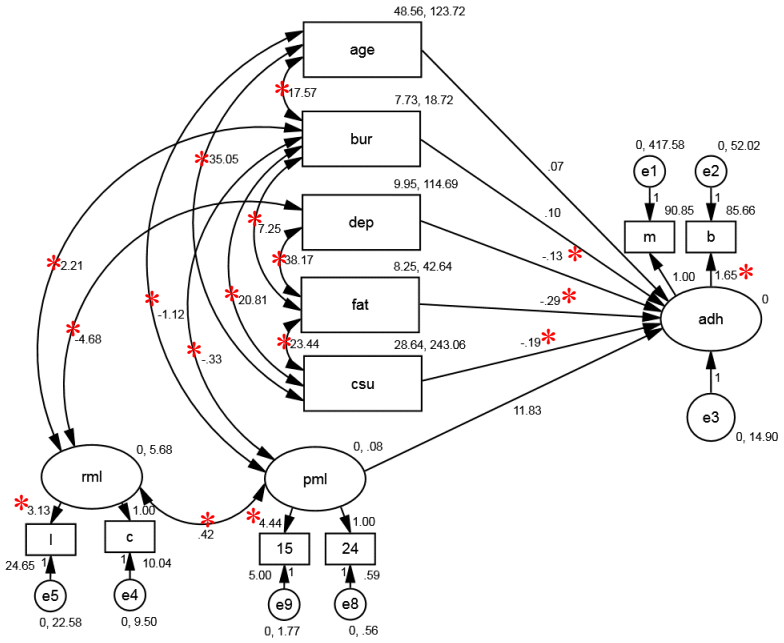


**Figure 13.** Covariate analyses (continued).

**C.**




**D.**

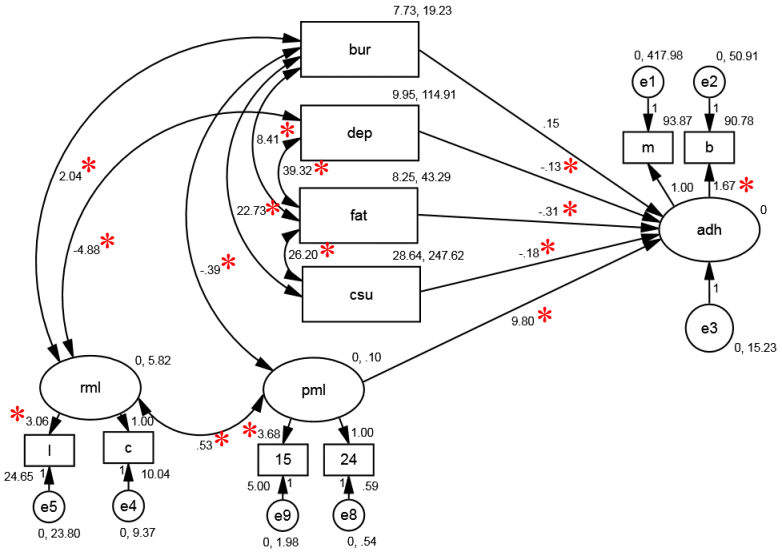
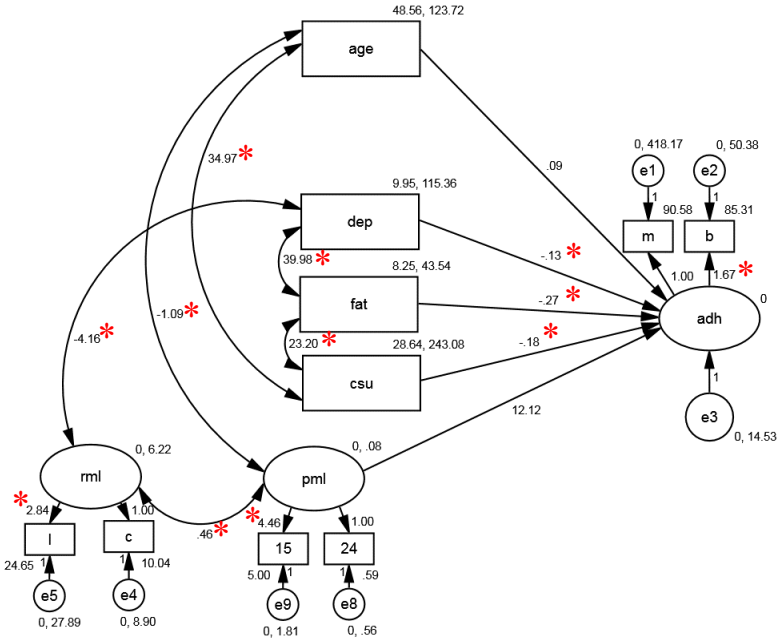


**Figure 13.** Covariate analyses (continued).

**E.**




**F.**

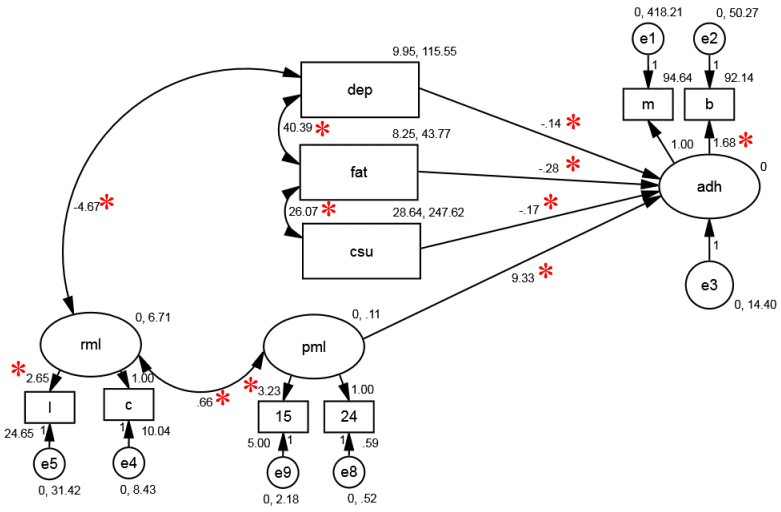
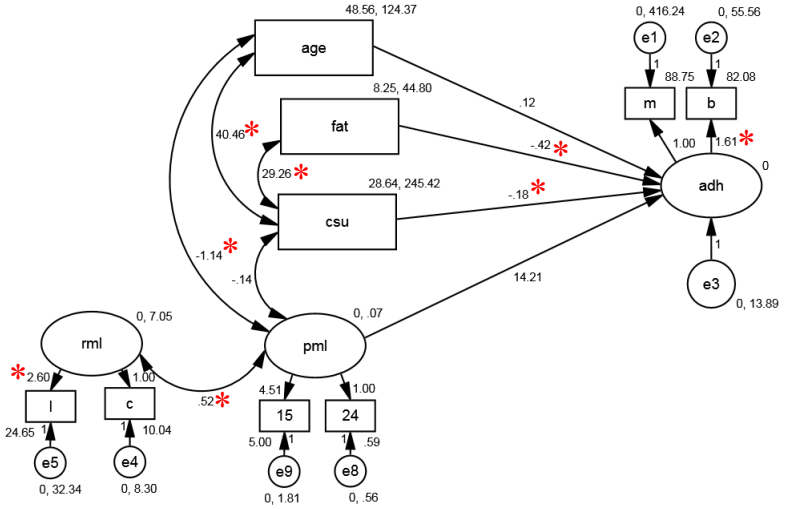


**Figure 13.** Covariate analyses (continued).

**G.**




**H.**

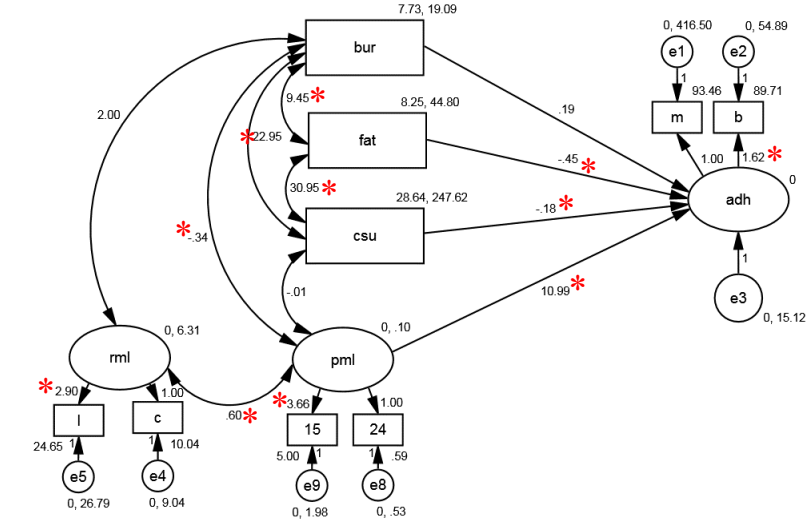
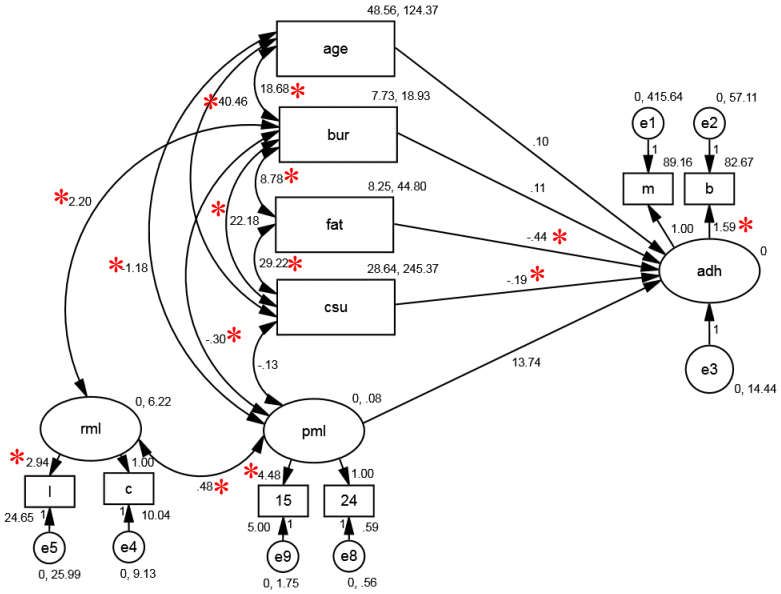
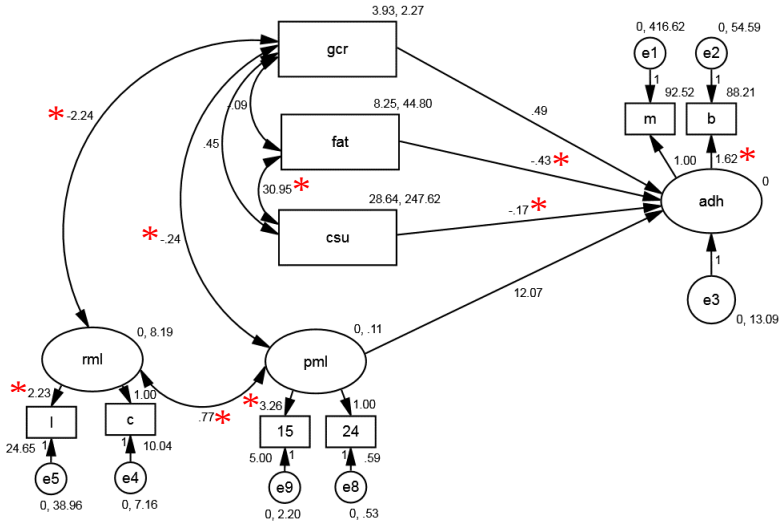


**Figure 13.** Covariate analyses (continued).

**I.**




**J.**




**K.**

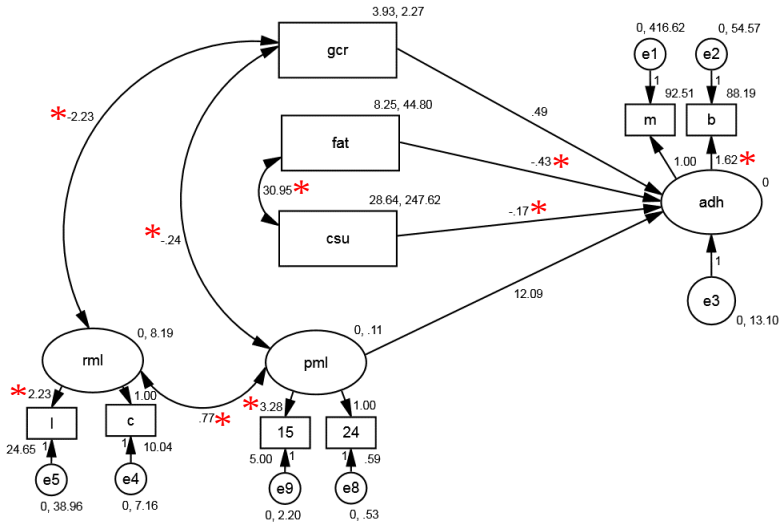


**Figure 13.** Covariate analyses (continued).

**Model Fit**

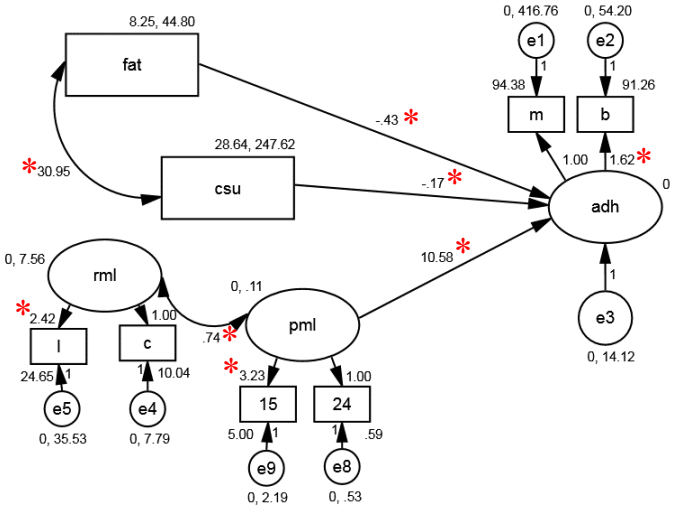
| | CMIN | DF | ***P*** | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **13A/8C** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **13B** | 34.587 | 26 | 0.121 | 1.33 | 0.924 | **0.955** | **0.979** | **0.043** | 136.587 |
| **13C** | 50.167 | 32 | 0.021 | 1.568 | 0.890 | 0.922 | **0.955** | **0.057** | 140.167 |
| **13D** | 32.324 | 26 | 0.183 | 1.243 | 0.919 | **0.969** | **0.982** | **0.037** | 110.324 |
| **13E** | 46.169 | 28 | 0.017 | 1.649 | 0.879 | 0.913 | 0.946 | 0.061 | 120.169 |
| **13F** | 26.984 | 22 | 0.212 | 1.227 | 0.921 | **0.973** | **0.984** | **0.036** | 90.984 |
| **13G** | 30.023 | 21 | 0.092 | 1.430 | 0.894 | 0.938 | **0.964** | **0.049** | 96.023 |
| **13H** | 24.264 | 19 | 0.186 | 1.277 | 0.920 | **0.963** | **0.980** | **0.040** | 94.264 |
| **13I** | 33.383 | 24 | 0.096 | 1.391 | 0.907 | 0.944 | **0.970** | **0.047** | 115.383 |
| **13J** | 20.459 | 20 | 0.430 | 1.023 | 0.929 | **0.997** | **0.998** | **0.011** | 88.459 |
| **13K** | 20.586 | 22 | 0.546 | 0.936 | 0.929 | **1.009** | **1.000** | **0.000** | 84.586 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Gray denotes significant chi-square results, one indicator of poor model fit.

**Fig.13. 13A:** Best-fitting Aim 1 model. **13B**: Default covariate model. **13C**: Removal of nonsignificant covariances. **13D**: Removal of age. **13E**: Removal of pill burden. **13F**: Removal of age and pill burden. **13G**: Removal of depression and pill burden. **13H**: Removal of age and depression. **13I:** Removal of depression. **13J:** Inclusion of global clinical rating score (gcr). **13K:** Removal of non-significant estimates. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). age: participant age. bur: total pill burden. csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. dep: depression from The Profile of Mood States Depression-Dejection subscale. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. gcr: global clinical rating score. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 14.** Depressive symptomatology as replacement for fatigue.

**A.**




**B.**

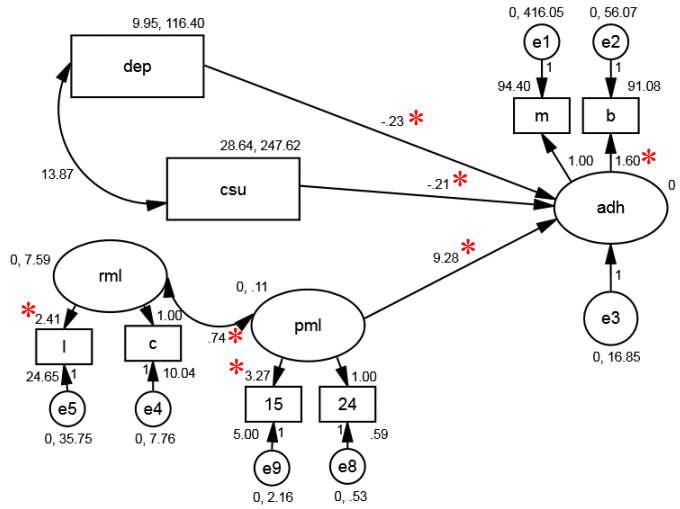
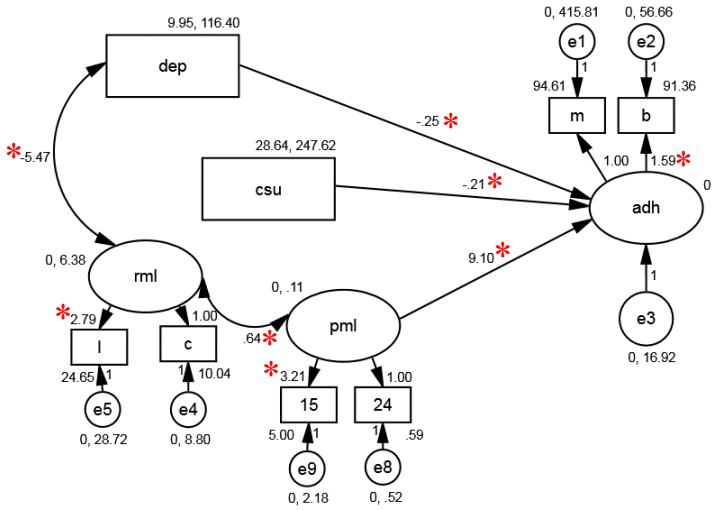


**Figure 14.** Depressive symptomatology as replacement for fatigue (continued).

**C.**




**Model Fit**

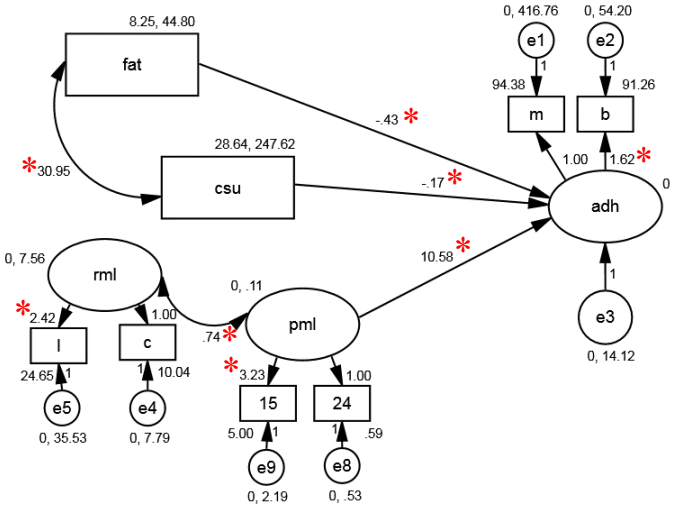
| | CMIN | DF | *P* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **14A/8C** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **14B** | 29.247 | 17 | 0.032 | 1.72 | 0.876 | 0.903 | 0.941 | 0.064 | 83.247 |
| **14C** | 25.168 | 17 | 0.091 | 1.48 | 0.893 | 0.935 | **0.961** | **0.052** | 79.168 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Gray denotes significant chi-square results, one indicator of poor model fit.

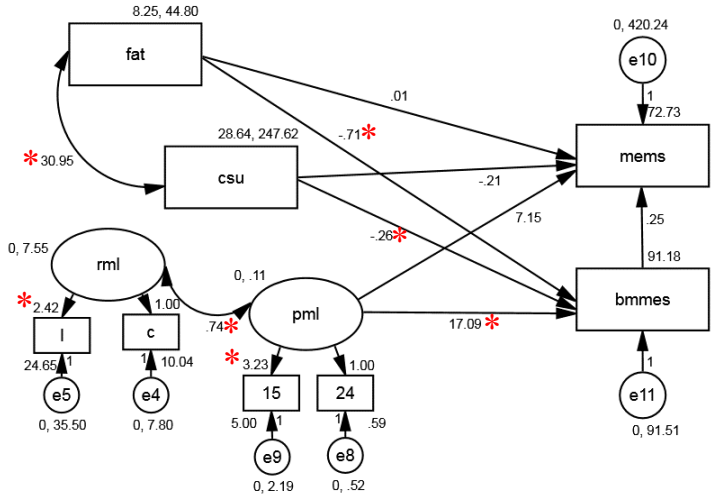
**Fig.14. 14A:** Best-fitting Aim 1 model. **14B**: Replacement of fatigue with depression. **14C**: Adjustment of covariances. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. dep: depression from The Profile of Mood States Depression-Dejection subscale. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 15.** Relationships between memory, fatigue, strategy use, perceived efficacy, and medication-taking behavior.

**A.**




**B.**




**C.**

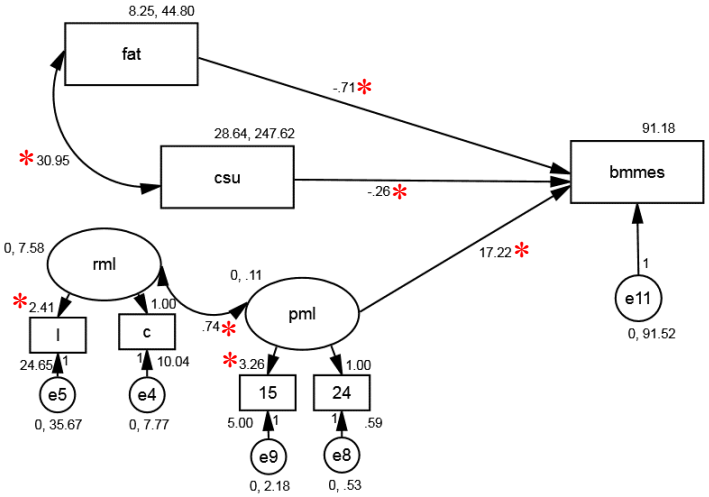
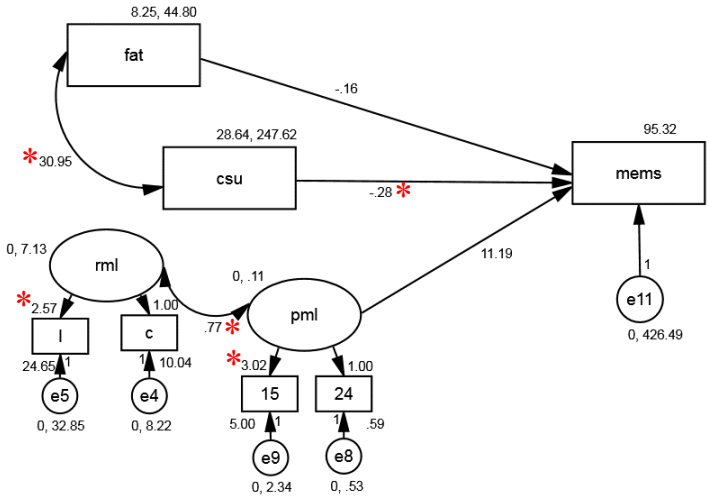


**Figure 15.** Relationships between memory, fatigue, strategy use, perceived efficacy, and medication-taking behavior (continued).

**D.**




**Model Fit**

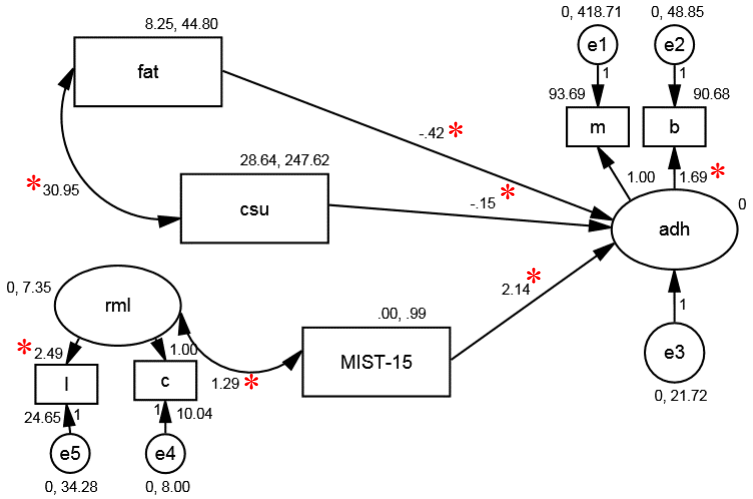
| | CMIN | DF | *P* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **15A/8C** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **15B** | 15.710 | 15 | 0.402 | 1.047 | 0.936 | **0.994** | **0.997** | **0.016** | 73.710 |
| **15C** | 15.247 | 12 | 0.228 | 1.271 | 0.934 | **0.973** | **0.984** | **0.039** | 61.247 |
| **15D** | 14.672 | 12 | 0.260 | 1.223 | 0.901 | **0.963** | **0.979** | **0.036** | 60.672 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit.

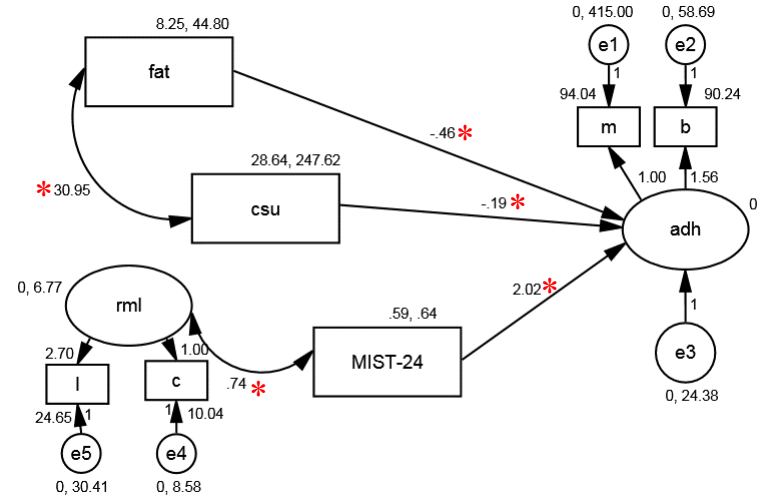
**Fig.15. 15A:** Best-fitting Aim 1 model. **15B**: Separation of adherence contributors from the latent variable. **15C**: Perceived efficacy alone. **15D**: Medication taking behavior alone. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (bmmes) and the medication event monitoring system (mems). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 16.** Effects of PM delay interval on the final model.

**B.**




**C.**



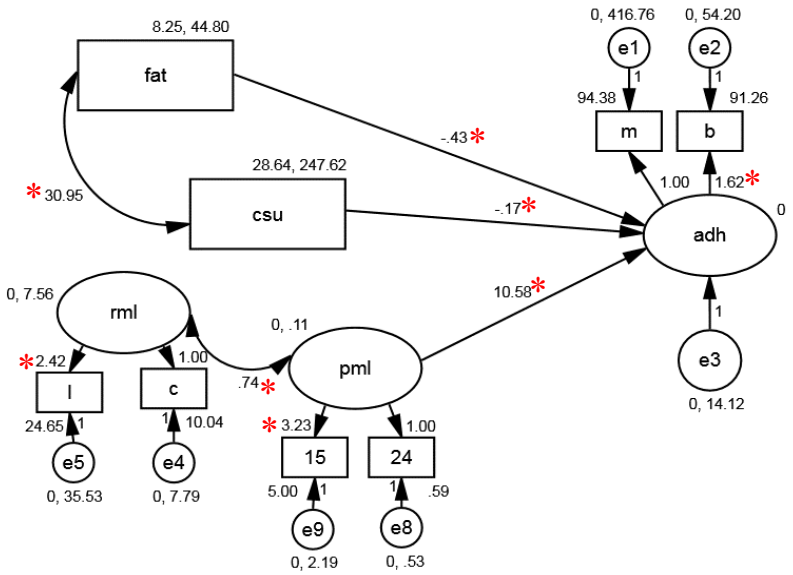

**Model Fit**

| | CMIN | DF | *P* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **16A/8C** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |
| **16B** | 19.175 | 12 | 0.084 | 1.598 | 0.912 | 0.936 | **0.963** | **0.058** | 65.175 |
| **16C** | 29.273 | 12 | 0.004 | 2.439 | 0.856 | 0.834 | 0.905 | 0.090 | 75.273 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Gray denotes significant chi-square results, one indicator of poor model fit.

**Fig.16. 16A:** Refers to the best-fitting Aim 1 model. **16B**: MIST-15 alone. **16C**: MIST-24 alone. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. MIST-15: Memory for Intentions Screening Test 15-minute delay subscore. MIST-24: Memory for Intentions Screening Test 24-hour delay subscore. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 17.** The aim 1 final model.



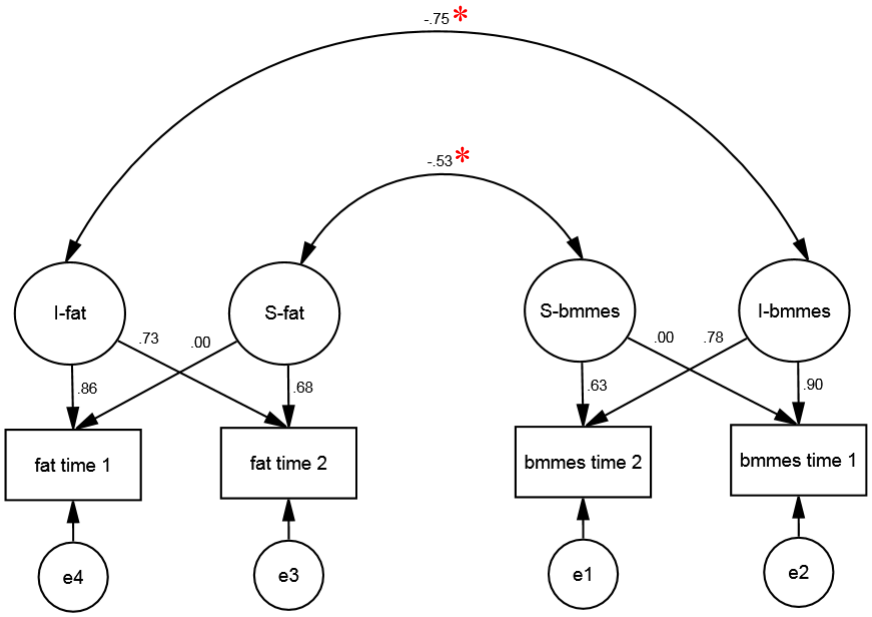

**Model Fit**

| | CMIN | DF | *P* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **17** | 17.594 | 17 | 0.415 | 1.035 | 0.929 | **0.996** | **0.997** | **0.014** | 71.594 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit.

**Fig.17.** Best-fitting Aim 1 model. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. adh: adherence latent variable of the Medication Management Efficiency Scale from the Beliefs Related to cART Adherence (b) and the medication event monitoring system (m). csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l).

**Figure 18.** Changes in fatigue and perceived efficacy.



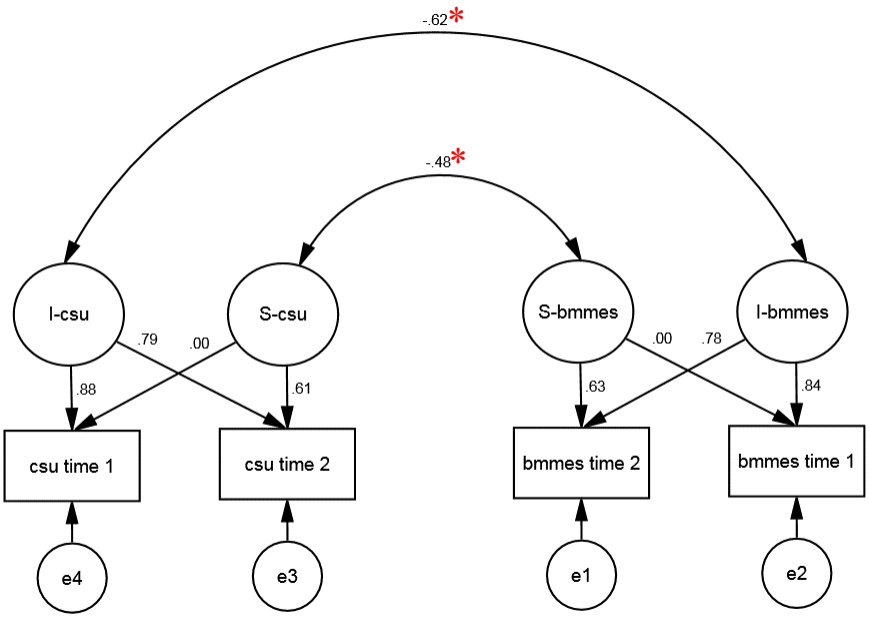

**Model Fit**

| | CMIN | DF | *P* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **18** | 5.615 | 2 | 0.060 | 2.807 | 0.941 | 0.878 | **0.959** | 0.180 | 21.615 |

***Note.*** Gray denotes significant chi-square results, an indicator of poor model fit.

**Fig.18.** Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. bmmes: perceived efficacy from the Beliefs Related to cART Adherence Medication Management Efficiency Scale. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. I: intercept. S: slope.

**Figure 19.** Changes in strategy use and perceived efficacy.




**Model Fit**

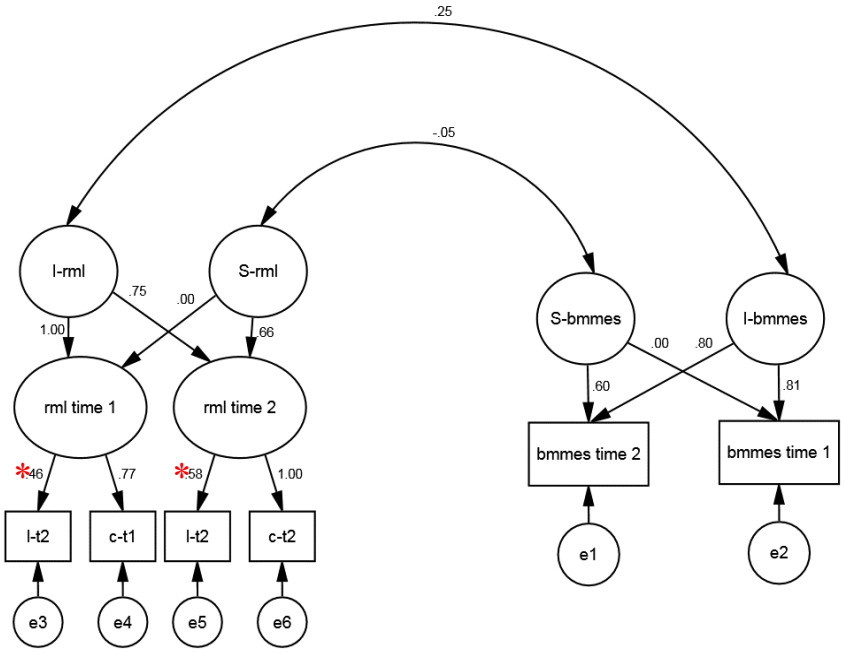
| | CMIN | DF | *P* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **19** | 1.429 | 2 | 0.489 | 0.714 | **0.985** | **1.020** | **1.000** | **0.000** | 17.429 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit.

**Fig.19.** Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. bmmes: perceived efficacy from the Beliefs Related to cART Adherence Medication Management Efficiency Scale. csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. I: intercept. S: slope.

**Figure 20.** Changes in memory and perceived efficacy.

**A.**




**B.**

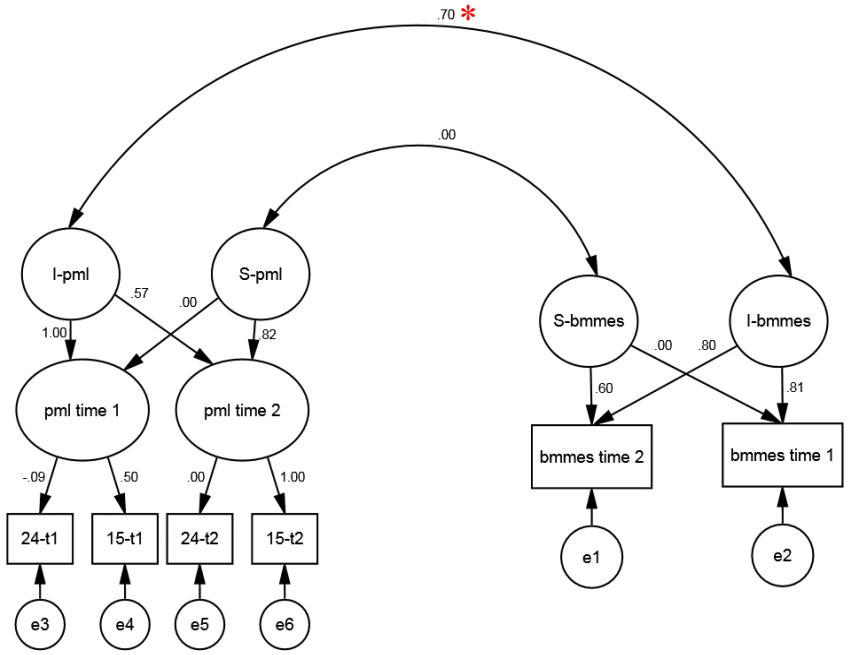
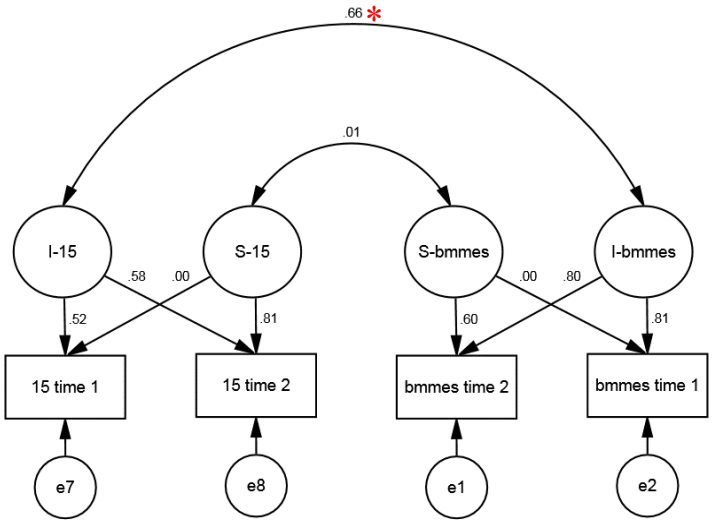


**Figure 20.** Changes in memory and perceived efficacy (continued).

**C.**




**D.**

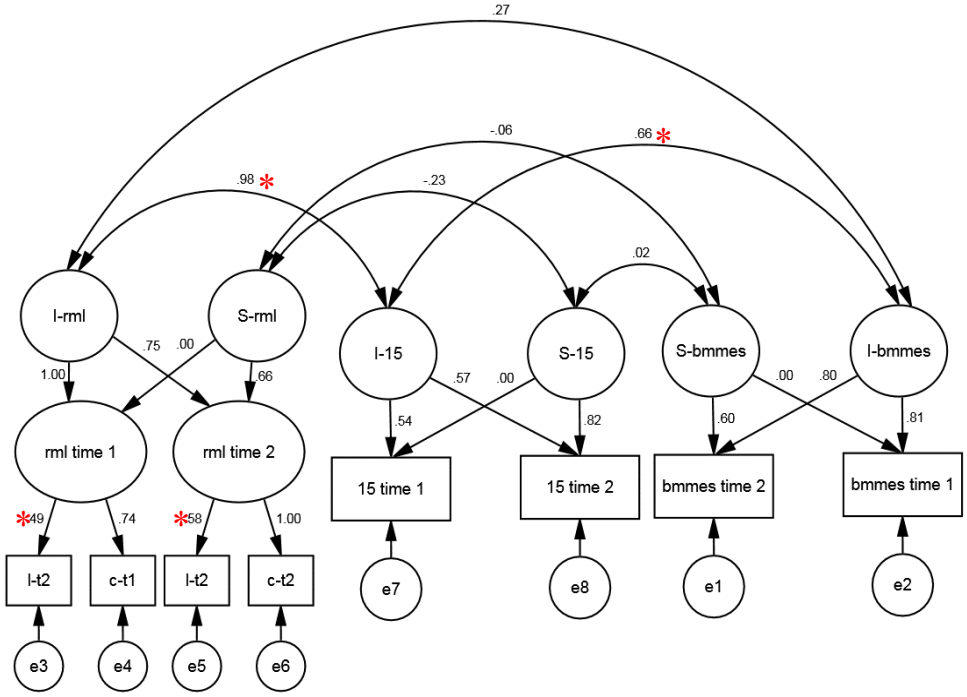


**Figure 20.** Changes in memory and perceived efficacy (continued).

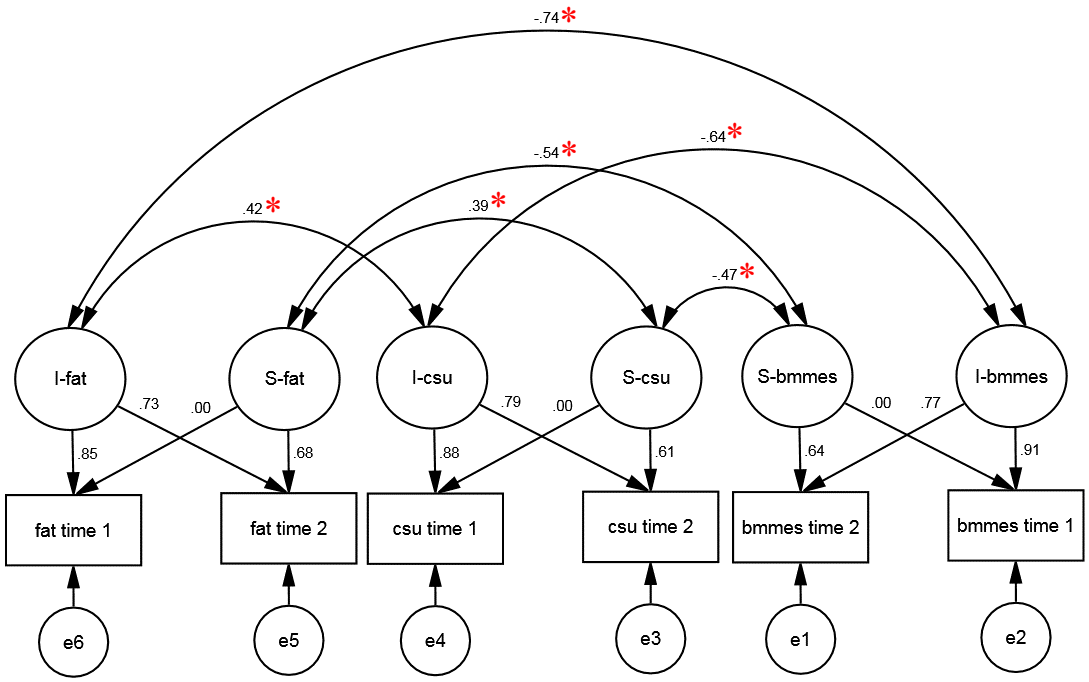
**Model Fit**

| | CMIN | DF | ***P*** | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **20A** | 26.225 | 9 | 0.002 | 2.914 | 0.773 | 0.714 | 0.828 | 0.185 | 50.225 |
| **20B** | 10.059 | 9 | 0.346 | 1.118 | 0.821 | **0.957** | **0.974** | **0.046** | 34.059 |
| **20C** | 0.037 | 2 | 0.982 | 0.018 | **0.999** | **1.148** | **1.000** | **0.000** | 16.037 |
| **20D** | 33.690 | 17 | 0.009 | 1.982 | 0.783 | 0.784 | 0.869 | 0.132 | 71.69 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Gray denotes significant chi-square results, an indicator of poor model fit.

**Fig.20. 20A**: RM and perceived efficacy. **20B:** PM and perceived efficacy. **20C**: MIST-15 and perceived efficacy. **20D**: RM, MIST-15, and perceived efficacy. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. bmmes: perceived efficacy from the Beliefs Related to cART Adherence Medication Management Efficiency Scale. e: residual error. pml: PM latent variable comprised of the MIST 15-minute (15) and 24-hour (24) delay trials. rml: RM latent variable comprised of the California Verbal Learning Test – II (c) and Logical Memory II (l). I: intercept. S: slope. t1: time 1. t2: time 2.

**Figure 21.** The aim 2 final model.




**Model Fit**

| | CMIN | DF | *P* | CMIN/DF | NFI | TLI | CFI | RMSEA | AIC |
|---|---|---|---|---|---|---|---|---|---|
| **18** | 5.615 | 2 | 0.060 | 2.807 | 0.941 | 0.878 | **0.959** | 0.180 | 21.615 |
| **19** | 1.429 | 2 | 0.489 | 0.714 | **0.985** | **1.020** | **1.000** | **0.000** | 17.429 |
| **20A** | 26.225 | 9 | 0.002 | 2.914 | 0.773 | 0.714 | 0.828 | 0.185 | 50.225 |
| **20B** | 10.059 | 9 | 0.346 | 1.118 | 0.821 | **0.957** | **0.974** | **0.046** | 34.059 |
| **20C** | 0.037 | 2 | 0.982 | 0.018 | **0.999** | **1.148** | **1.000** | **0.000** | 16.037 |
| **20D** | 33.690 | 17 | 0.009 | 1.982 | 0.783 | 0.784 | 0.869 | 0.132 | 71.69 |
| **21** | 6.601 | 6 | 0.359 | 1.100 | **0.958** | **0.990** | **0.996** | **0.042** | 36.601 |

***Note.*** **Bold** denotes model fit scores above peer-reviewed thresholds, thus indicating good model fit. Gray denotes significant chi-square results, an indicator of poor model fit. Model 21 is outline to indicate best model fit.

**Fig.21.** Other aim 2 model fit indices are presented for ease of best-fit comparisons. Single-headed arrows represent unstandardized path estimates. Double-headed arrows represent covariances. Estimates and covariances with *p* values <.05 are indicated with *s. bmmes: perceived efficacy from the Beliefs Related to cART Adherence Medication Management Efficiency Scale. csu: compensatory strategy use frequency from the Prospective Memory for Medications Questionnaire. e: residual error. fat: fatigue from The Profile of Mood States Fatigue-Inertia subscale. I: intercept. S: slope.