ABSTRACT

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	Jessica F. Magidson, Ph.D., 2013
Directed By:	Professor Carl W. Lejuez, Department of Psychology

Medication adherence is of utmost importance in predicting health outcomes across numerous chronic conditions, particularly HIV/AIDS. Highly active antiretroviral therapy (HAART) to treat HIV/AIDS requires high levels of adherence to maintain viral suppression, which is crucial for optimal HIV treatment and prevention. One of the most significant patient-level barriers to medication adherence is depressive symptoms. Even at subclinical levels, depressive symptoms predict nonadherence above and beyond other relevant psychosocial factors. Despite the focus on depressive symptoms as a reliable and powerful predictor of nonadherence, few studies have sought to test potential mechanisms underlying this relationship, which is an important step to advance our understanding of how depression affects adherence to inform intervention efforts. The current study utilized early behavioral theories of depression (Lewinsohn, 1974; Ferster, 1973) to select potential mediators that may be relevant to both depression and adherence. Specifically, we tested the key components of these models, (1) goal-directed activation, (2) positive reinforcement, and (3) punishment in one's environment as

potential mediators of the relationship between depressive symptoms and medication adherence among HIV positive individuals in substance abuse treatment (n = 73). We examined adherence to HAART as well as adherence to other daily medications using a combination of self-report assessments (% of doses missed over past four days, frequency of doses missed across common reasons for nonadherence) and viral load. Greater levels of punishment mediated a positive relationship between clinician-rated depressive symptoms and greater frequency of missed doses across common reasons for nonadherence. Activation and positive reinforcement were unrelated to adherence or viral load in this sample. Findings suggest the importance of punishment in explaining the relationship between depression and medication nonadherence. Individuals with elevated depressive symptoms may perceive greater negative consequences related to medications (e.g., side effects, stigma) and may be less likely to overcome barriers necessary for optimal adherence. If findings continue to replicate, this may suggest a need to target punishment in HIV prevention and treatment, for instance in the context of integrated cognitive behavior therapy interventions that target depression and adherence among substance users.

MEDIATORS OF THE RELATIONSHIP BETWEEN DEPRESSION AND MEDICATION ADHERENCE AMONG HIV POSITIVE SUBSTANCE USERS

By

Jessica F. Magidson

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Advisory Committee: Professor Carl W. Lejuez, Chair
Associate Professor Stacey B. Daughters, Co-Chair
Research Assistant Professor Laura MacPherson
Assistant Professor Lea Dougherty
Professor Elbert D. Glover

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Chapter 1: Introduction

Importance of Medication Adherence in HIV

Medication adherence is of utmost importance across numerous chronic medical conditions, and arguably most impactful on health outcomes and disease progression in HIV/AIDS. Indeed, highly active antiretroviral therapy (HAART) for the treatment of HIV/AIDS has substantially improved clinical outcomes, but only in the presence of consistent HAART use and nearly perfect rates of HAART adherence (Crum et al., 2006). Indeed, living with HIV/AIDS requires careful attention to medication adherence.

"Medication adherence" is defined in numerous ways in the literature, but most broadly refers to either medication doses missed completely (e.g., in the past four days, week, month, etc.) or doses taken earlier or later than the prescribed time (i.e., outside the appropriate time window). HAART regimens include a variety of medication types, including most commonly nucleoside reverse-transcriptase inhibitors (NRTIs), protease inhibitors (PIs), or more recently developed boosted PIs; all are taken daily, most often individuals are instructed to take medications twice daily (~67%) with a smaller percentage of individuals taking medications once daily or some three times daily (Genberg et al., 2011). Although medication instructions differ across drug classes, the majority are instructed to be taken at the same time each day, most preferably within a specific time window (e.g., 2-4 hours). Further, individuals are often taking other medication regimens for co-occurring medical and psychiatric comorbidities in addition to managing HAART regimens, which also require high levels of adherence (Cruess, Kalichman, Amaral, Swetzes, Cherry, & Kalichman, 2012).

How is it assessed? Medication adherence is assessed using a variety of methods, and given the document difficulties in accurately measuring adherence, researchers tend to compare different methods of adherence measurement, typically using self-report methods, an objective assessment (i.e., electronic pill caps), and HIV viral load as a clinical criterion of HAART adherence (Arnsten et al., 2001; Liu, Golin, Miller, Hays, Beck, & Sanandaji, 2001; Reynolds, 2004). Viral load has been most commonly selected as a clinical criterion, as it is considered the most proximal biological indicator of HAART adherence, with only the most optimal rates of HAART adherence leading to an undetectable amount of virus in the blood stream (i.e., <50 copies/mL) (Bangsberg et al., 2001; Bangsberg, 2006).

Numerous researchers have suggested that relying on solely one data source when measuring medication adherence will likely 'misrepresent the "true" rate of adherence' (Reynolds, 2004), as electronic pill caps tend to underestimate levels of adherence, while self-report measures tend to overestimate adherence. Further, electronic pill caps are often only utilized for a single medication and may not capture adherence across all pills in a regimen (Bova, Fennie, Knafl, Dieckhaus, Watrous, & Williams, 2005). There is some evidence that a summary or composite measure that combines two or more measures of adherence is more strongly related to clinical response than either measure alone (e.g., Farley, Hines, Musk, Ferrus, & Tepper, 2003; Liu et al., 2001); however, numerous other reviews have cautioned against summarization of data, as it may result in a loss of information of adherence patterns and a loss of power when investigating changes in adherence over time (Choo, Rand, Inui, Lee, Canning, & Platt, 2001; Reynolds, 2004).

Although newly developed modeling strategies and technologies continue to be developed to accurately assess adherence (e.g., Haberer et al., 2010), the most widely used measure of adherence remains self-report due to issues of cost and logistical feasibility (Simoni, Kurth, Pearson, Pantalone, Merrill, & Frick, 2006). Given the notable limitations of self-report assessment, including primarily the overestimation of adherence levels due to social desirability biases, it is recommended to utilize an additional measure of adherence that is more objective in nature, such as electronic pill cap technology or a biological indicator of therapeutic impact (i.e., HIV viral load; Reynolds, 2004). Although these three methods may be highly correlated, utilizing separate indicators of this difficult to assess behavior may be advantageous (Reynolds, 2004; Simoni et al., 2006). Additionally, regarding self-report assessment, guidelines have been developed to minimize social desirability biases, including framing questions to assume nonadherence, wording questions to normalize nonadherence, querying for reasons for nonadherence (as an alternative to asking directly about missed doses), as well as comparing self-report to other adherence measures to check for reliability (Miller & Hays, 2000; Simoni et al., 2006).

Why is it important, and how much "adherence" is enough? For HAART specifically, the minimum level of adherence required for clinical effectiveness is somewhat unclear and also may differ across drug classes; however, there is a well-established consensus that it is necessary to take a high proportion of HAART doses to maintain suppression of viral replication. Paterson and colleagues (2000) demonstrated that 78% of individuals who were ≥ 95% adherent showed suppressed viral load (to ≤ 400 copies/mL). Yet, these levels steeply decreased with even slightly lower levels of

adherence, such that if individuals were < 70% adherent, only 19% showed viral load ≤ 400 copies/mL. Even dropping to only 90-95% adherence, only 45% of individuals in this category achieved suppressed viral load (Paterson et al., 2000). More recently, evidence points to more potent drugs that have been developed (i.e., boosted PIs) as being more forgiving of nonadherence, such that they can suppress viral replication at more moderate levels of adherence (Bangsberg, 2006). However, high levels of adherence are still necessary (e.g., with boosted PIs, 92% of individuals achieved viral suppression with 78 to 93% adherence; Shuter, Sarlo, Kanmaz, Rode, & Zingman, 2007).

Do patients adhere? The strongest predictor of viral suppression is adherence, yet the proportion of individuals who achieve optimal adherence is often very small, ranging from 30% (Paterson et al., 2000) to as low as 4% (Golin et al., 2002). An important recently published study indicated that only 19% of all HIV-infected individuals nationwide showed undetectable viral load (i.e., <50 copies/mL), which is in a large part due to suboptimal adherence to HAART (Gardner, McLees, Steiner, del Rio, & Burman, 2011). A recent worldwide survey compared rates of adherence across countries and indicated that rates of adherence were the lowest in North America; 55% of patients in North America reported missing at least one dose in the past 30 days (Nachega et al., 2011). However, even when very high levels of adherence are not possible, a 10% increase in adherence can be associated with medically significant improvements in HIV outcomes (e.g., decreases in viral load; Bangsberg et al., 2001; Liu, Miller, Golin, Wu, Wenger, & Kaplan, 2006). Thus, although near perfect adherence is the optimal goal, incremental gains are also worth targeting.

Implications of nonadherence. Nonadherence and inconsistent patterns of adherence (e.g., interruptions in treatment, breaks from medication) have been associated with increased likelihood of production of medication-resistant HIV strains, greater health complications, failure to achieve full viral suppression (Bangsberg et al., 2001), and increased risk of death (Garcia de Olalla, Knobel, Carmona, Guelar, Lopez-Colomes, & Cayla, 2002). Although other pharmacological and biological causes can lead to drug resistance, missed HAART doses is the leading contributor to resistance. Drug resistance in particular is a significant public health issue, as individuals with persistent nonadherence will likely become resistant to existing medications and can also spread drug resistant strains of HIV to uninfected HIV individuals (Wainberg & Friedland, 1998). Indeed, adherence has important prevention implications, as recent work has also demonstrated that regular use of HAART by HIV positive individuals (as well as HIV negative individuals using Pre-Exposure Prophylaxis [PrEP]) may prevent HIV transmission, but these effects are only found among individuals with high levels of adherence (Cohen, 2010; Grant et al., 2010; Karim et al., 2010).

Monitoring adherence to other medications when patients are not receiving HAART

In addition to HAART nonadherence, lack of any HAART use (i.e., not being on HAART even when medically indicated) is also a critical factor that contributes to poor HIV/AIDS health outcomes and continued transmission of the virus. Despite the accessibility of HAART in the U.S., many patients are still not taking HAART; the Centers for Disease Control and Prevention report (CDC, 2011a) estimated that only 45% of individuals diagnosed with HIV are using HAART in the U.S. This may be due to a variety of reasons, including structural barriers and psychological factors (i.e., fear of side effects, stigma, fear of people knowing, substance use; Seekins, Scibelli, Juday, Stryker,

& Das, 2010). In particular, low-income, minority substance users have consistently been identified as a high risk group for not using HAART (Chander et al., 2009). Importantly, these groups may be at highest risk for HAART nonadherence once they do initiate a regimen, which, as stated earlier, has important implications related to future resistance to HAART regimens and poor health outcomes. As such, it has become an important priority for providers to monitor adherence to other daily medication regimens for patients who are not using HAART.

Supporting this perspective, adherence to other forms of medication (e.g., for other chronic medical conditions, psychotropic medication) or even placebo pills, has been shown to be one of the strongest predictors of future HAART adherence among individuals not receiving HAART (Cruess et al., 2012; Wagner, 2003). Indeed, adherence to other forms of medication tend to be highly correlated with HAART adherence (e.g., $r = .49$, $p < .001$; Wagner, 2003) and predict HAART adherence above and beyond other commonly related factors (e.g., recent medical appointment attendance, cognitive functioning, unstable housing, adherence self-efficacy; Wagner, 2003). Particularly among substance using populations, monitoring adherence to other forms of medication or placebo medication is common place to assess readiness for HAART, as providers may avoid prescribing substance users HAART to avoid numerous health risks that are likely if individuals do not adhere (Wagner, 2003). Studies have demonstrated that high adherence to other medications (i.e., psychotropic medication) is very strongly associated with high HAART adherence (Cruess et al., 2012; Horberg et al., 2008). In sum, examining adherence to other forms of medications among patients who are not on

HAART is extremely important given that these individuals may be at greatest risk for poor adherence once they initiate a HAART regimen (Chander et al., 2009).

Factors Associated with Medication Nonadherence

Numerous factors have been identified as being associated with medication nonadherence among HIV/AIDS patients; reviews on this topic have identified over 200 variables related to adherence, which are consistent across HAART adherence specifically as well as other forms of medication (Fogarty, Roter, Larson, Burke, Gillespie, & Levy, 2002). Fogarty et al. (2002) conducted a review of published and abstract reports on this topic and provided a comprehensive overview of factors related to medication nonadherence. This review grouped factors according to the following categories: factors related to the treatment regimen (regimen complexity, side effects), treatment- and medication-related attitudes and beliefs (e.g., fear and skepticism of the regimen, mistrust, myths of treatment effects), overall HIV disease attitudes (e.g., pessimism about HIV, worsening disease outcomes), scheduling demands (work, daily routine, mealtime dosing challenges), cognitive factors (difficulty concentrating, forgetfulness, inadequate information about medication), as well as many social and psychological factors such as psychiatric comorbidity (depression, anxiety, and substance use), and social climate (social support, confidentiality fears, disclosure). Institutional- and provider-specific variables were also identified as predictors of adherence, such as access to medication and health care, as well as provider support throughout treatment, perceived caring, and open communication with one's provider. Individual characteristics tested in relation to adherence included physical health status (hospitalization, symptomatic or clinical advancement of disease, disease progress, and health status

assessment), low socioeconomic status (education level, literacy, income, housing status, minority status), and demographic information (age, gender).

Similar categories of factors related to medication nonadherence have been identified in other reviews (e.g., Chesney, 2003; Reynolds, 2004) and include treatment characteristics (complexity, side effects), patient-related factors (lifestyle characteristics, psychosocial issues, psychological functioning, social support, health beliefs, substance use), factors related to the patient-provider relationship, and overall healthcare system-related factors (access to care, medications, informational resources). Regarding the patient-related factors, a high percentage of individuals simply forget their medication or have difficulty understanding regimen instructions (Chesney et al., 2000a) or have interfering psychosocial issues such as substance abuse, depression, stress, hopelessness, negative feelings, and poor social support (Chesney, Morin, & Sherr, 2000b; Gordillo, Del Amo, & Soriano, 1999; Holzemer et al., 1999; Paterson et al., 2000). These factors are relevant to HAART adherence specifically as well as adherence to other forms of medication among individuals with HIV (Cruess et al., 2012; Wagner, 2003). Of these factors, the most significant predictors of nonadherence that have been shown to be less easily mitigated through intervention include depression and stress (Chesney et al., 2000b; Gordillo et al., 1999; Paterson et al., 2000). Other studies examining psychological predictors of adherence have consistently demonstrated the important roles of depression, social support, treatment adherence self-efficacy, and substance use (Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000; Eldred, Wu, Chaisson, & Moore, 1998; Kalichman, Ramachandran, & Catz, 1999; Singh, Squier, Sivek, Wagener, Nguyen, & Yu, 1996).

Despite numerous factors identified as being related to medication nonadherence, there are few agreed upon variables that *consistently* predict adherence. Although the field has been able to identify correlates of nonadherence, experts in the field acknowledge that nonadherence is still poorly understood (Reynolds, 2004). Null findings are evident across almost all variables that report predictive associations, most notably for sociodemographic variables (gender, ethnicity, age, education, income, employment, and housing status) as well as substance use (Fogarty et al., 2002; Holzemer et al., 1999). As noted by Reynolds (2004), why an individual would not take their medication even when it may be lifesaving "belies simple explanations or demographics," and few factors reliably predict adherence.

As such, numerous researchers have pointed to the pressing need to focus research efforts on enhancing our understanding of those few predictors that consistently impact medication adherence. One such reliable predictor of nonadherence is depression. Depression has been shown to predict nonadherence across chronic medical conditions (DiMatteo, Lepper, & Croghan, 2000); among HIV positive individuals, depression predicts nonadherence above and beyond other reliable predictors, such as social support (Safren et al., 2001), stigma (DiIorio et al., 2009) and other psychiatric conditions (Waldrop-Valverde & Valverde, 2005). Further, depression as a barrier to adherence has received significant empirical and clinical attention given (1) its high prevalence among individuals with HIV/AIDS and (2) the link between depression and later HIV disease progression. In sum, as outlined in detail in the next section, depression is one of the few reliable predictors of adherence, and its impact on HIV outcomes represents a significant public health issue.

Depression is a Consistent Predictor of Medication Nonadherence

Although reviews have pointed to the fact that it is difficult to reliably predict medication adherence, the presence of depressive symptoms has been found to be one of the most consistent and significant predictors (Catz et al., 2000; Gordillo et al., 1999; Holzemer et al., 1999). The significant impact of depression on medication adherence is consistent with other types of chronic conditions; depression has been noted to be a barrier to adherence for patients with hypertension (Kim, Han, Hill, Rose, & Roary, 2003), coronary artery disease (Carney, Freedland, Eisen, Rich, & Jaffe, 1995), diabetes (Ciechanowski, Katon, Russo, & Hirsch, 2003), and kidney failure (Everett, Brantley, Sletten, Jones, & McKnight, 1995). Across these chronic conditions, depressed patients have been shown to be three times more likely to be nonadherent to medical regimens than non-depressed counterparts (see DiMatteo et al., 2000 for a meta-analysis).

Impact of depression on HAART adherence. Regarding HAART specifically, numerous studies have demonstrated depressive symptoms to have a powerful and consistent impact on adherence. A large multicenter trial found that 39% of nonadherent HIV positive individuals had clinically elevated depressive symptoms (assessed using the Montgomery-Asberg Depression Rating Scale [MADRS]) vs. only 17% of adherent individuals, and that only lower MADRS scores were associated with nonadherence to HAART in a final model (Starace et al., 2002). In another large-scale multi-site trial, Horberg and colleagues (2008) examined the effects of depression on HAART adherence among 3,359 patients at two large health maintenance organizations. In their sample, 42% of all patients had a depression diagnosis, and untreated depression was significantly associated with decreased odds of achieving ≥ 90% adherence. Another recent cohort study followed 225 individuals living with HIV/AIDS over a 2.5 year period and found

that those that developed depressive symptoms during the study period had worse adherence at a follow up (45.1% vs. 25.95%) vs. those who had not developed significant depressive symptoms; individuals with depressive symptoms were approximately two times more likely to have poor adherence over time (Kacanek, Jacobson, Spiegelman, Wanke, Isaac, & Wilson, 2010).

Depressive symptoms have been shown to be related to poor medication adherence over and above other psychosocial variables commonly related to adherence, such as social support, adherence self-efficacy, HIV-related attitudes (Safren, Otto, & Worth, 1999), neurocognitive impairment (Ammassari et al., 2004), patient satisfaction with provider, and stigma (DiIorio et al., 2009) as well as other psychiatric conditions and environmental factors (Waldrop-Valverde & Valverde, 2005). Studies have also sought to compare the impact of different psychiatric disorders on adherence; for instance Vranceanu et al. (2008) compared the impact of posttraumatic stress disorder (PTSD) and depression on HAART adherence and found that only depression contributed significant unique variance in predicting HAART adherence, suggesting a primary role of depression as a psychiatric disorder associated with poor adherence. Even at sub-threshold levels, depressive symptoms have a strong relationship with nonadherence; in a sample of substance users in methadone maintenance, a one-point increase in clinician-rated depressive symptoms (on the seven-point depression Clinical Global Impression Scale) was associated with a 75% increase in the odds of HAART nonadherence. Thus, even a moderate depression rating according to this scale would indicate almost a fivefold increase in the odds of nonadherence as compared to when no depressive symptoms are present (Gonzalez, Psaros, Batchelder, Applebaum, Newville, & Safren, 2011b).

High prevalence of depression in HIV. The impact of depression on adherence is particularly relevant to HIV given the extremely high prevalence of depression among individuals living with HIV. Depression is the most common psychological disorder among individuals with HIV **(**Bing et al., 2001; Chesney, 2003); estimates suggest that approximately 37% of patients infected with HIV meet criteria for a current depressive episode and 50% for a past history of major depression (e.g., Asch et al., 2003; Bing et al., 2001). Depression is thought to emerge following notification of initial HIV diagnosis and during periods of disease progression, as well as due to more constant stressors related to social, occupational, and sexual rejection, and "restrictions in activities that give meaning to life" (Starace et al., 2002).

A meta-analysis comparing HIV sero-positive individuals with HIV sero-negative individuals revealed HIV-infected individuals were almost twice as likely to be diagnosed with major depression compared to HIV sero-negative patients (Ciesla & Roberts, 2001). Morrison et al. (2002) found that major depression was four times higher in HIV-seropositive women compared to HIV-seronegative women. Further, the chances of acquiring depression are even higher among ethnic minorities and those living in poverty (Hasin, Goodwin, Stinson & Grant, 2005; Moneyham, Sowell, Seals, & Demi, 2000); rates of major depression have been shown to reach 72% among low-income, minority substance users with HIV (Berger-Greenstein, Cuevas, Brady, Trezza, Richardson, & Keane, 2007).

Consequences of depression and medication adherence: HIV disease progression. The effects of depression on HAART adherence have clear clinical consequences; depression has consistently been identified as a predictor of accelerated

HIV disease outcomes (largely due to its impact on medication adherence). Paterson et al. (2000) found a 40% increased risk of virologic failure in patients with active depression. Relatedly, depression has been associated with shorter survival among HIV positive individuals on HAART, such that individuals with depressive symptoms have shown to be almost six times more likely to die than adherent patients with no depressive symptoms (Lima et al., 2007). Another 7-year longitudinal study identified HIV positive individuals with depressive symptoms to be two times more likely to die compared with those with limited or no depressive symptoms (Ickovics et al., 2001). The impact of depression on HAART adherence has warranted significant empirical and clinical attention given its link to later HIV disease progression and increased risk of mortality (Gore-Felton & Koopman, 2008; Leserman et al., 2002).

How Does Depression Impact Medication Adherence?

Despite the focus on depression as a reliable and powerful predictor of medication nonadherence across chronic health conditions and among individuals with HIV specifically, few studies have sought to test potential mechanisms underlying the relationship between depression and medication nonadherence. A recent meta-analysis and review of the relationship between depression and HAART adherence (n = 35,029; 95 independent samples) noted that "although many studies have examined "whether" depression is associated with treatment nonadherence in HIV/AIDS, none of the included studies examined "how" depression is related to nonadherence" (Gonzalez et al., 2011a, p. 186). To date, numerous studies have focused on testing medication adherence as a mediator of the relationship between depression and disease progression (Gore-Felton & Koopman, 2008); yet, the potential mechanisms underlying the first piece of this model—

how depression impacts adherence—have not been tested adequately, and further, not in a high-risk sample of low-income, minority substance users. This recently published meta-analysis (Gonzalez et al., 2011a) pointed specifically to the need for "more research that examines the potential mechanisms linking depression and treatment nonadherence in HIV/AIDS to develop more focused interventions," (p. 186). Relatedly, another recently published commentary also noted that there is a pressing need to identify "underlying psychological processes" that account for the impact of depression on HAART adherence as well as other forms of medication adherence in HIV (Kagee, 2012).

Importance of understanding the impact of depression on adherence.

Identifying potential mechanisms underlying the relationship between depression and medication adherence can advance our understanding of *how* depression interferes with adherence in order to inform intervention efforts. This is particularly important currently, as there has been an increasing focus in the field on developing integrated treatments (i.e., to target both depression and adherence simultaneously; Daughters, Magidson, Schuster, & Safren, 2010; Safren et al., 2009; 2012; Soroudi et al., 2008). Improving our understanding of how depression affects adherence has the potential to increase the effectiveness of these interventions as well as to better match intervention efforts to patient needs, particularly for patients with psychiatric comorbidity. This is sorely needed given that less than 20% of individuals in the U.S. living with HIV/AIDS demonstrate optimal health outcomes (Gardner et al., 2011), increasing risks of mortality, drug resistance, and continued HIV transmission (Cohen, 2010; Grant et al., 2010; Karim et al., 2010) particularly among individuals with depression (Leserman et al., 2002; Lima et

al., 2007). In sum, although depressive symptoms have been identified as a prevalent and powerful barrier to adherence, particularly among substance users, no studies to date (e.g., *n* = 35,029; 95 independent samples included in a recent meta-analysis; Gonzalez et al., 2011a) have examined *how* depression is related to nonadherence, which is crucial "to develop more focused interventions" (Gonzalez et al., 2011a; p. 186).

Potential Mediators of the Relationship between Depression and Adherence

Selecting potential behavioral mediators of the relationship between depression and adherence requires a careful consideration of theory and relevance to medication adherence. Additionally, research has pointed to the importance of identifying *behavioral* mediators in advancing our understanding of adherence, particularly given that behavior can be more easily altered with intervention, and secondly, regarding HAART adherence specifically, the most commonly cited reasons for nonadherence are behavioral (Chesney, 2003; Palmer, Salcedo, Miller, Winiarski, & Arno, 2003). Thus, consideration of potential mediators of the relationship between depression and adherence in the current proposal stems closely from behavioral theories of depression that are also closely relevant to existing research on medication adherence.

Behavioral theories of depression. Behavioral models of depression may offer insight into identifying potential behavioral mediators of the relationship between depression and medication adherence. Early behavioral theories of depression developed by Lewinsohn (1974) and Ferster (1973) suggest that depression is characterized by a few key components: (1) goal-directed activation; (2) the degree of positive reinforcement available in one's environment; and (3) the extent to which an individual experiences punishment in one's environment.

Regarding the first component, goal-directed activation, behavioral theories of depression posit that depression results from a change in specific behavioral patterns, such that individuals engage in fewer goal-directed or meaningful activities/behaviors, either in terms of quantity (the number or intensity of these behaviors) or the quality (diversity of types of activities, associated meaning or purpose; Ferster, 1973; Lewinsohn, 1974). This is supported by early work using the Pleasant Events Schedule (PES; MacPhillamy & Lewinsohn, 1971), which demonstrated that depressed, non-depressed, psychiatric, and normal controls all exhibited a positive relationship between mood level and frequency of pleasant activities (Lewinsohn & Graf, 1973; Lewinsohn & Libet, 1972). Depressed individuals engaged in fewer pleasant activities and reported less pleasure from these activities (Lewinsohn & Graf, 1973; MacPhillamy & Lewinsohn, 1971); in particular, depressed individuals lacked engagement in interpersonal behaviors, thereby suggesting they may have been receiving less social reinforcement (Lewinsohn & Shaffer, 1971).

The second and third components, the degree to which an individual experiences reinforcement and punishment in one's environment, are related to a combination of factors. Recent evidence suggests that the probability of experiencing reinforcement may be closely related to a person's ability to obtain or elicit reinforcement, including necessary skills (e.g., social skills) to engage in behaviors that may be reinforced. Further, this likelihood is influenced by the availability of potentially reinforcing events, one's history of being exposed to punishing or aversive experiences, as well as the presence of suppressors or punishers in one's current environment. In sum, obtaining reinforcement is associated with a combination of factors that increase as well as reduce

the probability of reinforcement in one's environment (Carvalho et al., 2011; Lewinsohn, 1974; Lewinsohn, Sullivan, & Grosscup, 1980).

Relevance of Behavioral Theories of Depression to Medication Adherence in HIV/AIDS

The main components of behavioral theories of depression (Ferster, 1973; Lewinsohn, 1974), (1) goal-directed activation, (2) positive reinforcement in one's environment, and (3) punishment in one's environment, may hold particular relevance to medication adherence in HIV/AIDS. Although these relationships have not yet been tested directly (i.e., between goal-directed activation and adherence, or positive reinforcement/punishment in one's environment and adherence), other lines of evidence suggest that these changes in behavior- and reinforcement-related patterns may be associated with medication adherence. Next, we review lines of evidence suggesting that these core components of behavioral theories of depression may hold particular relevance to understanding medication adherence in HIV/AIDS.

Goal-directed activation and medication adherence. Numerous lines of research have suggested that one's patterns of activity engagement may be particularly important in predicting medication adherence (Chesney et al., 2000a; Gifford, Bormann, & Shively, 2000; Roberts, 2000; Wenger et al., 1999). Lifestyle characteristics and "patterns of regular behaviors and activities" (Wagner & Ryan, 2004), including changes in daily routine and ability to fit a regimen into a daily routine, have consistently been identified as important factors related to medication adherence, including HAART, other forms of medication, and even placebos (Chesney et al., 2000a; Gifford et al., 2000; Roberts, 2000; Wagner & Ryan, 2004; Wenger et al., 1999). Indeed research has

demonstrated that engaging in regular, daily activities predicted medication adherence over and above other factors commonly related to adherence (gender, diagnostic status, patient-provider relationship, psychological stress, and perceived treatment efficacy).[1]

Further, this may also depend on the type of activity, such as social-related activities or employment. Wagner & Ryan (2004) found that regarding social activities, "active social networks" seem to interfere with medication adherence, yet social support is consistently identified as a facilitator to adherence. Depression-related research has suggested that reduced social interaction in particular may limit opportunities for emotional and practical support necessary for adherence (Starace et al., 2002). Mixed findings have also been identified regarding how employment impacts adherence (Chesney et al., 2000a; Wagner & Ryan, 2004). To date, this line of work has largely been limited to the practical and logistical aspects of activity engagement (e.g., routine, location of activities). Studies rarely have also captured the *quality* of these activities, for instance the purpose of the activities (e.g., goal-directed nature) or reward associated with these activities, which may be important in clarifying mixed findings.

Positive reinforcement in one's environment and medication adherence. Various lines of evidence suggest that positive reinforcement in one's environment may be important to inspire continued motivation for self-care behaviors. For instance, studies focusing on contingency management approaches to medication adherence have identified that other forms of reinforcement may be necessary for continued adherence, as medication adherence provides little positive reinforcement for immediate behavior; rather, individuals are more likely experience aversive consequences (e.g., side effects,

[1] Please see Appendix A for a detailed description of the studies (i.e., Ryan & Wagner, 2003; Wagner & Ryan, 2004) that assessed daily routinization and medication adherence.

others noticing them taking medication, reminder of HIV status; Chesney, 2003; Chesney et al., 2000a). As such, other forms of positive reinforcement in one's environment may be necessary to drive continued motivation for self-care and overall motivation to "engage in self-care activities designed to prolong one's life" (Berger-Greenstein et al., 2007; Ryan & Wagner, 2003). Holzemer et al. (1999) examined predictors of adherence across diverse clinical settings in seven U.S. cities (n = 420) and found that the only significant predictors of adherence were self-reported depressive symptoms and one specific component of a quality of life assessment labeled "cherishing the environment" (measured using a 38-item scale of quality of life among individuals with HIV/AIDS; Wilson, Hutchinson, & Holzemer, 1997). The cherishing the environment subscale was composed of items related to "having a meaningful life," "feeling comfortable and well-cared for," "using time wisely," and "taking time for important things." This element of quality of life—how an individual interacts with his/her environment in a meaningful way—is closely tied to behavioral theories of depression and the types of behaviors that are typically reduced among individuals with depression. Yet, this has not yet been tested as a mechanism underlying the relationship between depression and medication adherence.

Punishment in one's environment and medication adherence. One's history of being exposed to punishing or aversive experiences and the presence of punishers/suppressors in one's environment also may be relevant to medication adherence. Exposure to punishing or aversive experiences is closely linked to an external locus of control of reinforcement, referring to the degree to which individuals expect that reinforcement or a particular outcome is contingent on their own behavior or personal

characteristics (Rotter, 1975). Indeed, there is great overlap between these two constructs, such that individuals with an external locus of control are more likely to report experiencing punishing or aversive experiences and believe their behavioral choices will not lead to subsequent reinforcement (Hiroto, 1974; Rotter, 1966). An external locus of control is strongly implicated in depression (Benassi, Sweeney, & Dufour, 1988) and health-related behaviors; numerous lines of research have demonstrated that one's locus of control predicts patterns of adherence across chronic conditions, such as diabetes (Schlenk & Hart, 1984) and hypertension (Stanton, 1987), and evidence also has suggested locus of control may be related to medication adherence and HIV-related self-care (Aversa & Kimberlin, 1996; Evans, Ferrando, Rabkin, & Fishman, 2000). As such, the specific component of Lewinsohn's theory related to one's perception of being exposed to punishing or aversive experiences, which has been strongly linked to depression, may also be implicated in adherence.

In sum, although the specific components of early behavioral theories of depression have not been tested in relation to medication adherence, numerous lines of evidence suggest their relevance to adherence. Further, these components of Lewinsohn's theory may be potential mediators of the relationship between depression and medication adherence, which to date, has not been tested.

Substance Users as High Risk Group to Target for HIV, Depression

Understanding the relationship between depression and medication adherence may be most critical to substance abusing HIV positive populations, as HIV positive substance users have been shown to display the highest rates of depressive symptoms (Berger-Greenstein et al., 2007). Both substance use and HIV have been shown to significantly increase the likelihood of having major depression (Hasin et al., 2005;

Moneyham et al., 2000). Among low-income, minority HIV positive substance users living in urban areas, research has indicated the extremely high rates of major depression (i.e., reaching up to 72%; Berger-Greenstein et al., 2007). Further, even sub-threshold levels of depressive symptoms are highly correlated with nonadherence in this population; for instance, a one-point increase in clinician-rated symptoms was associated with a 75% increase in the odds of HAART nonadherence among active substance users in methadone maintenance (Gonzalez et al., 2011b).

In addition to high rates of depression in this group and the demonstrated impact of depressive symptoms on adherence, low-income minority substance users living in urban areas are also an important group to target because they bear the burden of a more recent shift in the HIV/AIDS epidemic. Recent epidemiological statistics on the HIV/AIDS epidemic indicate that African Americans account for almost half of people living with HIV in the U.S. and nearly half of new infections in the U.S. (CDC, 2011b); further, examining incidence rates by transmission category from 1985 through 2009, heterosexual contact is the only mode of HIV transmission that has continued to be on the rise (CDC, 2011b), which is largely among African Americans and suggested to be intertwined with a substance using lifestyle (i.e., sex with an injection drug user or exchange of sex for drugs or money common among crack/cocaine users; CDC, 2007). In the District of Columbia specifically, which reports the highest rate of new HIV/AIDS cases in the U.S. (120 AIDS diagnoses per 100,000 per population, five times greater than the other states reporting the highest rates of HIV/AIDS in the U.S; CDC, 2011b), the most notable increase in new HIV cases has been among substance users, specifically non-injection crack/cocaine users (Kuo et al., 2011). An overwhelming majority of these

cases are African Americans, who represent 95% of cumulative cases in this population (Ngamsnga & Wright-Andoh, 2004). Heterosexual contact (i.e., sex with a person with or at high risk for HIV infection, primarily injection drug users, and exchange of sex for drugs or money particularly among crack/cocaine users), is the leading mode of transmission among African Americans in Washington D.C. (32.4%; DC Department of Health, 2010) and a leading driver of the continued epidemic in the area (Kuo et al., 2011). Finally, this is also a very important group to target based on disparities in health outcomes; low-income, minority, HIV positive substance users often demonstrate poor HIV health outcomes, primarily due to poor HAART adherence or not using HAART at all (Chander et al., 2009).

In sum, across the U.S. as well as in D.C. specifically, HIV incidence has shifted from primarily high rates among men who have sex with men (MSM) to more "socially vulnerable" and "disenfranchised populations," including low-income minority groups with comorbid mental health conditions and other types of substance use disorders (beyond only injection drug use) such as crack/cocaine dependence (Mellins et al., 2009). Individuals suffering from depression, substance use problems, and HIV follow a more chronic and treatment-resistant course than those with only one disorder (Cook, Grey, & Burke-Miller, 2004) and warrant particular attention given the changing epidemic.

Current Study

The current study aimed to improve our understanding of potential mechanisms underlying the impact of depression on medication nonadherence among low-income HIV positive substance users. We used a theoretically-driven approach to test behavioral mediators of the relationship between depression and medication adherence drawn from

Lewinsohn and Ferster's early behavioral models of depression. The three main aims, outlined below, examined the key components of these models, (1) goal-directed activation, (2) positive reinforcement, and (3) punishment in one's environment as potential mediators of the relationship between depressive symptoms and medication adherence. We assessed adherence to HAART as well as adherence to other daily medications. The overall aim was to illustrate how specific behavioral patterns common in depression may explain the powerful relationship between depression and medication adherence in a high-risk sample of substance users living with HIV/AIDS.

Primary Aims and Hypotheses

(1) **Aim 1:** Test goal-directed activation as a mediator of the relationship between depressive symptoms and medication adherence.
    a. *Hypothesis 1:* Goal-directed activation will mediate a negative relationship between depressive symptoms and medication adherence (see Figure i for directionality across all aims).

(2) **Aim 2:** Test positive reinforcement in one's environment as a mediator of the relationship between depressive symptoms and medication adherence.
    a. *Hypothesis 2:* Positive reinforcement in one's environment will mediate a negative relationship between depressive symptoms and medication adherence.

(3) **Aim 3:** Test punishment in one's environment as a mediator of the relationship between depressive symptoms and medication adherence.
    a. *Hypothesis 3:* Punishment in one's environment will mediate a negative relationship between depressive symptoms and medication adherence.

Exploratory Aim

(1) **Exploratory Aim 1:** Consider the potential mediators together to test whether the mediating effects are limited to a single variable or each provides incremental prediction. (see Figure i for a conceptual model of all study aims).

Chapter 2: Method

The current study tested the relationships between depressive symptoms, depression-related behavioral patterns, and medication adherence among substance users living with HIV/AIDS. Behavioral variables were derived from longstanding behavioral theories of depression (Lewinsohn, 1974; Ferster, 1973) that hold particular relevance to medication adherence. The main components of these models include (1) goal-directed activation, (2) positive reinforcement in one's environment, and (3) punishment in one's environment, each of which was hypothesized to be significantly correlated with adherence. Next, we aimed to examine these variables as potential mediators of the relationship between depressive symptoms and medication adherence and to assess whether these variables independently or together mediated the relationship between depressive symptoms and medication adherence.

Medication adherence was assessed for HAART specifically as well as other daily medications prescribed (psychotropic medications, cardiovascular medications, diabetes medications, anticonvulsants, and hormones). We used two methods to assess both adherence to HAART and adherence to other forms of medication. For "HAART adherence" specifically, we examined: (1) Self-reported ratio of doses missed over the past four days, and (2) Viral load -- a clinical indicator of adherence among individuals

on HAART (n = 47). For "all medication adherence," we examined: (1) Self-reported ratio of doses missed over the past four days, and (2) Frequency of reasons endorsed for medication nonadherence in the total sample (n = 73). Each measure of adherence was considered separately as the main outcome across analyses.

Recruitment

Participants for this study were first recruited as part of an ongoing randomized control trial (RCT) evaluating ACT HEALTHY (Daughters et al., 2010), an integrated behavioral activation based intervention (Daughters et al., 2008; Magidson et al., 2011) combined with Life-Steps (Safren et al., 1999), examining effects on depression, substance use, and medication adherence. The current study was drawn from the baseline data of this trial, conducted prior to randomization to treatment condition and the start of the study intervention. Recruitment for this trial ended in September of 2011, and to meet the sample size requirements of the current study, 15 additional participants were recruited (baseline assessment only) using an addendum to the larger trial protocol. All procedures for the baseline assessment remained the same.

All participants were recruited from the Salvation Army Harbor Light Substance Abuse Treatment Center in Northeast Washington, D.C. The center requires complete abstinence from drugs and alcohol, with the exception of caffeine and nicotine; regular drug testing is provided and any use is grounds for dismissal from the center. When needed, detoxification from an outside source is required prior to entry into the center. Aside from scheduled activities (e.g., group retreats, physician visits), residents are not permitted to leave the center grounds during treatment. Although patients at the facility

often meet criteria for a dual diagnosis, treatment for mental health problems other than substance use is typically not available, and the treatment center does not have a psychiatrist on staff. Patients with psychiatric problems receive substance abuse treatment at this center but off-site health centers are utilized to provide pharmacological treatment (~25% of patients).

Participants had to meet the following inclusion criteria: 1) minimum of 18 years of age; 2) complete detoxification as needed prior to entry into the center and/or be drug free for at least one week prior to study participation; and 3) diagnosed with HIV/AIDS. Patients were excluded if they did not meet all inclusion criteria or if they met diagnostic criteria for a current psychotic disorder (as measured by the SCID-IV; First & Gibbon, 2004). For the current study, participants were excluded from all analyses if they were not prescribed any daily medication, which was necessary to assess medication adherence.

The importance of protecting participant confidentiality greatly influenced our recruitment strategy. Specifically, the administrative office of the treatment center was aware of patients' HIV status, and they approached HIV positive residents and asked if they were interested in hearing about a research study conducted by our team, which was independent of their status and treatment at Harbor Light. We were extremely sensitive to the potential for coercion. We provided no advantage to the administrative staff in referring clients to us. Further, staff members were informed that clients often do not meet inclusion criteria, so they were unable to determine if a referred patient not participating declined participation or was ineligible. It is notable that we regularly conduct other treatment and research studies at the center, thus individuals were not

automatically labeled as “HIV positive” if others saw them spending time with our research team. Further, patients who were not HIV positive were not informed that an HIV-specific study was being conducted.

If individuals were interested in participating, they were invited for an initial interview and screening assessment to confirm their eligibility. The screening assessment included the Structured Clinical Interview for the DSM-IV (SCID-IV; First & Gibbon, 2004) and a brief medical questionnaire. Individuals who did not meet criteria or who were ineligible based on data obtained during interviews were excluded from the study. Participants who met criteria were provided written informed consent and participated in the baseline assessment session, which took place during individuals’ first two weeks at the substance abuse treatment center. As our team has been doing at Harbor Light (for the past 9 years), assessment sessions occurred during the patients’ free time on either Tuesday evening or Friday afternoon so as not to interfere with treatment. All assessment measures proposed in the current study were included in an existing protocol approved by the University of Maryland Institutional Review Board (IRB). To reduce attrition, monetary incentives were used. Participants were compensated 20$ in gift cards for completing the assessment.

Participants

Eighty participants met all inclusion criteria for the current study. Three declined participation, and four were excluded from current analyses because they were not prescribed any type of daily medication regimen, which was not included in the exclusion criteria for the larger trial but necessary to assess medication adherence in the current

study. Of the final sample (n = 73), 94.5% of the sample was African American, 71.2% heterosexual, 50.7% female, and the mean age was 45.0 (*S.D.* = 7.8). Regarding psychopathology, the most prevalent disorders in the sample included current major depressive disorder (MDD; 17.8%), lifetime MDD (45.2%), bipolar I disorder (15.1%), lifetime posttraumatic stress disorder (PTSD; 19.2%), past year crack/cocaine dependence (54.8%), past year alcohol dependence (32.9%), past year opioid dependence (24.7%), and antisocial personality disorder (ASPD; 27.8%). The remaining disorders assessed (all anxiety disorders, other substance use disorders, and borderline personality disorder) were of less than 15% prevalence in the current sample. In total, 64.4% (n = 47) of the current sample was prescribed HAART, and 35.6% (n = 26) was not prescribed HAART (based on self-report and medical records). Tables i and ii provide more information on demographics, Axis I and II psychopathology, health status, and health-care related factors for the total sample and broken down by HAART use.

Assessment Measures

Measures were organized into six domains: (a) demographics, psychopathology, and medical history to determine eligibility and considered as covariates in analyses; (b) depressive symptoms, both self-report and clinician-rated, included as separate independent variables (IVs) across all Aims; (c) measures of goal-directed activation and positive reinforcement/punishment in one's environment, included as the potential mediators across all Aims; (d) medication adherence (for both HAART and other daily medications) assessed using self-report methods and biological measurement of viral load for individuals on HAART, which were the primary outcome measures across all Aims; and (e) health status, which was also considered as a potential covariate across all Aims.

a) Demographics, psychopathology, medical history

Demographics form assessed age, race/ethnicity, education level, marital status, employment status, and annual household income.

The *Structured Clinical Interview for the DSM-IV* (SCID-IV; First & Gibbon, 2004) was used to assess lifetime and current DSM-IV Axis-I psychopathology and select Axis II disorders including borderline personality disorder (BPD) and antisocial personality disorder (ASPD). The SCID was conducted by trained interviewers (graduate students and post-baccalaureate research assistants) during participants' first week at the substance abuse treatment center as part of a screening for eligibility.

The *Medical Questionnaire* was a brief questionnaire administered at the SCID interview that assessed history of chronic medical conditions (including HIV) and daily medication use. This information was verified with Center records and used to determine study eligibility.

b) Depressive symptoms

The *Beck Depression Inventory* (BDI-II; Beck, Steer, Ball, & Ranieri, 1996) is a 21-item self-report measure of depressive symptoms. Sample items include "sadness" and "loss of pleasure." Higher scores suggest increased depression severity. The instrument has excellent internal consistency (α =.92) with depressed younger and older adults (Beck et al., 1996; Nezu, Ronan, Meadows, & McClure, 2000). The BDI-II was used as a measure of depressive symptoms as an IV across all aims.

The *Hamilton Depression Rating Scale – 7 item version* (HAMD-7; Maier & Phillip, 1985) is a clinician-rated measure of severity of depressive symptoms. Clinicians rate each of the 7 items on a scale of 0-4 with higher scores indicating increased depression severity. Sample items include "Have you been feeling down or depressed this past week? How often have you felt this way, and for how long?" and "In the past week, have you felt guilty about something you've done, or that you've let others down?" Previous research has shown that the measure has strong internal consistency (α =.84) and excellent convergent validity with the Montgomery-Asberg Depression Rating Scale (MADRS) (r = .90; McIntyre et al., 2005). The HAMD was assessed as a measure of clinician-rated depressive symptoms as an IV across all aims.

Given that discrepant scores have often been noted when correlating self-report and clinician-rated assessment more generally (i.e., using the HAMD and BDI; Bailey & Coppen, 1976; Enns, Larson & Cox, 2000; Sayer et al., 1993) and among HIV positive substance users specifically (Gonzalez et al., 2011b), we examined each measure of depressive symptoms in separate analyses and treated them as separate IVs for all Aims.

c) *Goal-directed activation and positive reinforcement/punishment in one's environment*

Goal directed activation: The *Behavioral Activation for Depression Scale* (BADS; Kanter, Mulick, Busch, Berlin, & Martell, 2007) measures the frequency of activation, escape, and avoidance behaviors outlined in behavioral theories of depression. The 25-item measure includes a four factor scale (Activation, Avoidance/Rumination, Work/School Impairment, and Social Impairment). "Activation" assesses "goal-directed

activation" and completion of scheduled activities (for example, "I engaged in a wide and diverse array of activities" and "I did something that was hard to do but it was worth it"). The "Avoidance/Rumination" subscale measures avoidance of negative aversive states and engaging in rumination rather than active problem solving (e.g., "I did things to avoid feeling sadness or other painful emotions," "I tried not to think about certain things"). The "Work/school impairment" subscale represents inactivity and passivity regarding work and school responsibilities (e.g., "I took time off of work, or other responsibilities simply because I was too tired or didn't feel like going in,") and "Social impairment" reflects inactivity and passivity regarding social activities (e.g., and "I was withdrawn and quiet, even around people I know well"). Higher scores indicate greater activation and lower impairment/avoidance across all subscales. The BADS has been demonstrated to have strong internal consistency (α = .92) and good test-retest reliability (r = .74) in depressed and non-depressed samples (Kanter et al., 2007; Kanter, Rusch, Busch, & Sedivy, 2009). In the current sample, internal consistency for the total score and four subscales ranged from acceptable to good (Activation: α = .80; Avoidance/Rumination: α = .86; Work/School Impairment: α = .79; Social Impairment: α = .72; BADS total score: α = .85). The BADS was used to test the mediating role of goal-directed activation.

Positive reinforcement/punishment in one's environment: *The Reward Probability Index* (RPI; Carvalho et al., 2011) measures the degree of positive reinforcement and punishment in one's environment and was developed specifically in line with Lewinsohn's model of depression. The RPI has 20 items and a two-facture structure, which includes "Reward Probability" and "Environmental Suppressors." The Reward

Probability subscale consists of 11 items related to the number of potential reinforcers and an individual's ability to obtain reinforcement through instrumental behaviors. Example items in this subscale include "It is easy to find good ways to spend my time" and "I have the abilities to obtain pleasure in life." Higher scores indicate greater probability of reward in the environment. The Environmental Suppressors subscale includes 9 items that assess availability of potential reinforcers and the presence of aversive stimuli in the environment. Example items include "I have had many unpleasant experiences" and "It seems like bad things always happen to me." Items in this subscale are reverse scored, and higher scores on this subscale indicate lower levels of punishment in one's environment. The RPI has been demonstrated to have strong internal consistency ($\alpha = .90$), test-retest reliability ($r = .69$), convergent validity (with strong correlations between the RPI and measures of activity, avoidance, reinforcement, and depression [$r = .65$ to $.81$]), and discriminant validity (with smaller correlations between the RPI and measures of social support and somatic anxiety [$r = -.29$ to $-.40$]). In the current sample, internal consistency for the total score and the two subscales ranged from acceptable to good (Environmental Suppressors: $\alpha = .70$; Reward Probability: $\alpha = .86$; RPI Total Score: $\alpha = .79$). The RPI Reward Probability subscale was used to test the mediating role of positive reinforcement in one's environment, and the RPI Environmental Suppressors subscale was used to test the mediating role of punishment.

d) Medication Adherence: All medications and HAART adherence specifically

We assessed both adherence to all daily medication regimens, including HAART, psychotropic medications, cardiovascular medications, diabetes medications,

anticonvulsants, and hormones in the total sample (n = 73), as well as adherence to HAART specifically only among participants taking HAART (n = 47).

Self-reported medication adherence: We used a widely utilized self-report measure of medication adherence, the *ACTG Adherence to Antiretroviral Medication Questionnaire* (Chesney et al., 2000a), to measure medication adherence for all medications. Participants began by reading a set of directions that highlight how difficult it is for many patients to adhere to various medication regimens, providing support for truthful answers that acknowledge both adherent as well as nonadherent behavior. Next, participants provided the following information for each of their medications (HAART and all non-HIV medications): (1) name of drug; (2) prescribed doses per day; (3) prescribed number of pills per dose; and (4) any special directions, such as 'with food', 'on an empty stomach' or 'with plenty of fluids.'

Four-day adherence ratios (for all medications and HAART specifically): Participants were next asked about the pills that they took for each of the last four days, including the name of each medication and how many pills they had missed that day. This information was used to create two separate sets of ratios of doses missed vs. doses prescribed over the past four days for 1) HAART specifically; and 2) all daily medications.

Frequency of reasons endorsed for nonadherence: In the last section of the ACTG (Chesney et al., 2000a), participants were presented a list of 14 reasons why people may ever miss taking their medications (e.g. being away from home, busy with other things, simply forgot) and were asked "how often have you missed taking your medications

because you…" for each reason. Participants rate responses on a four-point scale (never, rarely, sometimes, often) to indicate the frequency of nonadherence due to each of the 14 reasons. The responses were summed to create a total score of frequency of reasons endorsed for medication nonadherence, with higher scores indicating greater frequency of reasons endorsed for nonadherence. There is no specified time frame for this part of the ACTG.

Querying for reasons for nonadherence has been recommended as a way to minimize potential biases of self-report when assessing adherence, including inaccurate recall and social desirability, as is wording questions in a way that assumes nonadherence (Simoni et al., 2006). This method has been used in other studies as a main adherence outcome as a means to capture a wider time frame for nonadherence beyond the past four days and minimize potential inaccuracies of self-reported adherence (O'Cleirigh, Ironson, & Smits, 2007; DiIorio et al., 2009). We did not distinguish between HAART and other types of medications when assessing reasons for nonadherence and thus only examined the frequency of reasons endorsed for nonadherence for all medications (as opposed to examining reasons endorsed for nonadherence of HAART specifically). In the current sample, internal consistency for the nonadherence reasons subscale was excellent $\alpha = .90$.

Biological indicator of HAART adherence: We also assessed a common biological indicator of medication adherence, *Viral Load*, which is a measure of the amount of HIV virus in the bloodstream and represents a more objective measure of HAART adherence for individuals on HAART. Viral load has repeatedly demonstrated a significant correlation with HAART adherence (Arnsten et al., 2001; Glass et al., 2006; Paterson, et al., 2000), with only the most optimal rates of HAART adherence being

associated with an undetectable amount of virus in the blood stream (i.e., <50 copies/mL). Viral load has been selected most commonly as a clinical criterion to reflect adherence, as it is considered a more proximal indicator of adherence (i.e., compared to CD4 count; Safren et al., 2009; Simoni et al., 2006). Specifically, we obtained consent from all participants to receive copies of their blood work information from their medical provider (within -60/+30 days from assessment). When blood work was not scheduled during this time, participants were requested to get it taken (which was clearly outlined in the patient consent form). In the current sample, participants on average had received blood work 9.57 days before the assessment (*S.D.* = 30.35 days). Given the high skew of viral load values in the literature and in the current sample (skewness = 4.08, *SE* = 0.29), viral load was log10 transformed for all analyses, which is the most common approach to analyzing viral load data in the field.

In sum, in measuring medication adherence for the current study, we used two measures of "all daily medication adherence": (1) Ratio of doses missed over the past four days; and (2) Frequency of reasons endorsed for nonadherence score; and two measures of "HAART adherence" specifically: (1) Self-report (ratio of doses missed over the past four days); and (2) Clinical indicator of adherence (viral load), which is in line with clinical recommendations in the field (e.g., Miller & Hays, 2000; Reynolds, 2004). We treated each measure of medication adherence as a separate dependent variable (DV) across all Aims.

e) <u>Health Status</u>

Self-reported health status was assessed using the *Quality of Life: SF-36* (Ware, Kosinski, & Keller, 1994), which is a self-report measure of overall physical and mental health functioning. The SF-36 examines quality of life in multiple dimensions: general health, physical functioning, role-physical, bodily pain, vitality, social functioning, role-emotional, mental health, and reported health transitions, and two summary scales can be computed: a physical health and mental health status total score. The measure has been widely used and validated across numerous health settings and patient populations (McHorney, Ware, & Raczek, 1993; McHorney, Ware, Lu, & Sherbourne, 1994; Ware & Gandek, 1998). Biological health status was assessed using CD4 count, a measure of immune system functioning and disease progression. This was obtained from participants' medical records of the most recent blood work appointment (-60/+30 days from current assessment) in line with the procedure stated above for obtaining viral load. Participants also self-reported *Years since HIV Diagnosis* and basic health care-related characteristics, such as whether they reported having a primary care physician (PCP) and a health insurance plan. All health status measures were considered as potential covariates across all Aims.

See Table 1 for a list of measures by domain and time point.

Table 1. List of assessment measures by domain at each study assessment session.

Assessment	*Screening*	*Assessment*
Demographics and Psychopathology		
Demographics Form		X
SCID-IV	X	
Medical Questionnaire	X	
Depressive Symptoms		
BDI-II		X
HAMD		X
Activation, Reinforcement/Punishment		
BADS		X
RPI		X
Medication Adherence (All medications)		
Ratio of doses missed in past 4 days		X
Frequency of reasons endorsed for nonadherence		X
HAART adherence		
Ratio of doses missed in past 4 days		X
Viral load		X
Health Status		
SF-36		X
CD4 Count		X
Years since HIV Diagnosis		X

Data Analytic Plan Overview

Sample size considerations

We based our sample size needs on effects published in studies related to depression, environmental/activation-related variables, and medication adherence that tested closely related variables, as well as effects observed in our pilot data in this area. Regarding relationships between the independent variable (depressive symptoms) and mediators (goal-directed activation, positive reinforcement/punishment in one's environment), published reports have demonstrated medium to large effect sizes for both the relationship between goal-directed activation and depressive symptoms (r = -.72; Kanter et al., 2009) and the relationship between positive reinforcement/punishment in one's environment and depressive symptoms (r = -.74; Carvalho et al., 2011). Regarding the relationship between the mediators (goal-directed activation and positive reinforcement/punishment in one's environment) and the dependent variable (medication adherence), effect sizes were drawn from related studies examining the relationship between daily activity engagement and medication adherence, as well as pilot data in this area (Daughters et al., 2010), all pointing to medium to large effect sizes (r = -0.44 to -0.63) (Wagner & Ryan, 2004). Regarding the relationship between the IV, depressive symptoms, and the DV, medication adherence, recent work examining depressive symptom severity and medication nonadherence in a sample of HIV positive substance users observed a large effect size (Cohen's d = 0.98; Gonzalez et al., 2011b). According to Fritz & MacKinnon (2007), the necessary sample size for partial mediation to have a power of 0.80 using an alpha of 0.05 (Cohen, 1988) is approximately 54 to 71 for

medium to large effect sizes (0.39 to 0.59 for the alpha and beta paths) using bias-corrected bootstrapping. Thus, we proposed 75 participants to test for mediation and to plan for refusal and dropouts.

Statistical analyses overview

There were numerous steps in our data analytic plan. All data first were double-entered, compared, cleaned, and verified for accuracy. For all continuous variables, we examined distributional properties and checked for outliers by examining skewness and kurtosis. This was of particular concern for the dependent variables (viral load, past four day adherence ratios), and our approach for handling the high skew of these variables is detailed below.

We next identified potential covariates for analyses by examining the relationship between the set of theoretically driven covariates identified a priori, including demographic and health status-related variables, and the dependent variables. Given the high skew of viral load values in the literature and in the current sample (skewness = 4.08, *SE* = 0.29), viral load was log10 transformed for all analyses, which is the most common approach to analyzing viral load data in the field. We also examined viral load categorically among individuals on HAART, comparing individuals based on detectable viral load status (VL $\leq$ or $>$ 50). Given the main focus on medication adherence in the current study and that not all participants were prescribed HAART, we also compared individuals using HAART vs. not using HAART to assess any group differences in these same covariates to be overly conservative when identifying potential covariates. Finally, given that recruitment continued beyond the completion of the larger trial (an additional

15 participants were recruited to meet the sample size needs for the current study), we also compared these 15 individuals to the remainder of the sample recruited from the larger trial on all key variables.

As the first step to plan for mediation analyses, we conducted two separate correlation matrices to identify candidate mediators. We first examined the correlations between both measures of the IV (HAMD, BDI), potential mediators (subscales of the BADS and RPI), and frequency of reasons endorsed for all medication nonadherence for the total sample (n = 73). We then conducted a correlation matrix examining the relationship between the IVs, potential mediators, and viral load only among individuals on HAART (n = 47). A variable was considered as a potential mediator in subsequent analyses if there was a significant association between one of the IVs and the potential mediator (*a* path), and the mediator(s) and the DV (*b* path). There has been some debate in the literature as to whether the direct relationship between the IV and DV (*c* path) needs to be significant for mediation; in order to identify any potential indirect effects that may not rely on the direct effect of the IV on the DV, we also considered potential indirect effects even if the IV and DV were not significantly related, as recommended by Hayes (2009).

We next conducted two sets of analyses to test for mediation. We first ran a series of linear regression analyses to test whether the four criteria set by Baron & Kenny (1986) were met, if there was (1) a significant direct effect of the IV on the DV; (2) a significant effect of the IV on the potential mediator; (3) a significant effect of the mediator on the DV; and (4) whether the effect of the IV on the DV after controlling for

the mediator was no longer significant but the effect of the mediator remained significant in the model.

Second, we also utilized non-parametric bootstrapping to test for significance of the indirect effect, which is recommended for small samples, because there are no assumptions about the shape of the sampling distribution of the indirect effect (Preacher & Hayes, 2004). Bootstrapping is based on resampling with replacement which is done many times (e.g., 5,000 times) to generate an empirical approximation of the sampling distribution of the indirect effect (Hayes, 2009). In these analyses, the indirect effects are significant if the 95% bias-corrected or percentile-based confidence intervals (CIs) for the indirect effect do not include 0 (Preacher & Hayes, 2004; Preacher et al., 2007). Given that the mean of the bootstrapping distribution will not precisely equal the indirect effect, both endpoints of the CIs are typically corrected for bias. However, there has been some controversy regarding bias-corrected bootstrapping tests being too liberal (Fritz, Taylor, & MacKinnon, 2012). As such, we utilized both the bias-corrected and percentile-based 95% CIs to interpret the significance of indirect effects and examined whether 0 was included in either CI. Given that the current study was cross-sectional, we also ran the proposed mediation models switching the mediator and DVs to demonstrate that the DV was not also mediating the relationship between the IV and proposed mediators (Preacher & Hayes, 2004). Given the potential bi-directionality of this relationship (i.e., improvements in adherence resulting in improvements in depressive symptoms), we also ran the proposed mediation models switching the IV and DV.

Chapter 3: Results

Overview of Medication Adherence in Current Sample

As indicated above, 64.4% (n = 47) of the current sample was prescribed HAART (based on self-report and medical records). Participants on HAART were taking an average of 3.22 HIV medications per day (*S.D.* = 1.84). In the total sample, participants were taking an average of 5.84 medications per day (*S.D.* = 3.50). 41.7% of the sample was taking cardiovascular drugs, 40.3% antidepressant medication, 16.7% anticonvulsant medication, 13.9% diabetes medication, and 4.2% were taking daily hormones. Of individuals on HAART, 97.8% were prescribed an NRTI, 58.7% a PI, 26.1% integrase inhibitors, 2.2% entry fusion inhibitors, 2.2% NNRTIs, and 21.7% a combination pill of NRTI and NNRTIs (i.e., Atripla).

Rates of medication adherence

We assessed adherence to all daily medication regimens, including HAART, psychotropic medications, cardiovascular medications, diabetes medications, anticonvulsants, and hormones, as well as adherence to HAART specifically only for patients that were on HAART (n = 47). We calculated adherence ratios (i.e., doses taken vs. doses prescribed for each participant) for both HAART specifically and all daily medications for the total sample. For HAART specifically, mean adherence rates ranged from 94.57% to 100% in the past four days for HAART; HAART adherence rates were 100% yesterday, 94.57% two days ago, 97.83% three days ago, and 97.83% four days ago. Regarding all medications, mean adherence rates ranged from 94.93% to 97.74% in

the past four days; all daily medication adherence rates were 97.33% yesterday, 94.93% two days ago, 96.51% three days ago, and 97.74% four days ago.

There was little variability in rates of nonadherence over the past four days, and more specifically a ceiling in rates of nonadherence was present. All adherence ratios were highly skewed (skewness statistics < -4.5 for all ratios), which was not improved following transformations. As such, we could not utilize these ratios as main outcome variables for adherence. Instead, we focused on the two other main adherence outcome variables assessed – viral load (for individuals on HAART) and frequency of reasons endorsed for nonadherence for all medications – that captured a greater time frame of nonadherence and also did not ask for patients to report on missed doses directly, which previous research has noted is susceptible to inflated adherence rates (Kalichman et al., 2009; Simoni et al., 2006).

Frequency of reasons endorsed for nonadherence was in the normal range for skew and kurtosis and was not transformed. Responses ranged from 0 to 36, and the mean in the current sample was 11.97 (*S.D.* = 9.42). Mean log10 viral load for the total sample was 2.40 (*S.D.* = 1.08). For individuals on HAART, mean log10 viral load was 1.98 (*S.D.* = .83).

Identifying potential covariates

Covariates Related to DV

As indicated above, we first identified any potential covariates that were related to either of the DVs (frequency of reasons endorsed for nonadherence or viral load). The set of theoretically-relevant covariates were selected a priori based upon previous research

indicating their relevance to medication adherence and viral load, including a range of demographic and health status-related variables. None of these factors were significantly related to frequency of reasons for medication nonadherence (all *ps* > .05). CD4 count was related to log10viral load and was identified as a covariate for all subsequent analyses that used viral load as the DV (see Table iv for all relationships between potential covariates and both DVs).

Covariates that Differentiate Individuals on HAART vs. Not

Given the main focus on medication adherence in the current study and that not all participants were prescribed HAART, we also compared individuals taking HAART vs. not taking HAART to assess any group differences in demographics, psychopathology, health status, or health-related characteristics that would be important to control for in analyses (see Tables i and ii). We also examined group differences in levels of depressive symptoms (the IV), activation, positive reinforcement, and punishment (the potential mediators), and medication adherence (the DV), comparing individuals using HAART vs. not using HAART to ensure equivalence across groups for these key variables (see Table iii). As indicated in these tables, the only significant difference (at $p < .05$) across groups was in viral load; specifically, individuals on HAART had significantly lower viral load compared to individuals not on HAART ($t(63) = -6.56$, $p < .0001$). This difference in viral load was expected as a direct result of HAART use. Given that we are examining viral load as an indicator of HAART adherence only among individuals on HAART, this would not impact the analyses and was not included as a covariate. We also compared the additional 15 participants that were recruited following completion of the larger trial to the rest of the sample from the

larger trial on all key variables. There were no significant differences across groups on any potential covariate or other key variables for analyses (all *p*s > .15).

Identifying Potential Mediators

As the first step to plan for mediation analyses, we next conducted two correlation matrices to identify candidate mediators. We first examined the correlations between both measures of the IV (HAMD, BDI), potential mediators (BADS, RPI), and the DV (frequency of reasons endorsed for nonadherence to all medications) in the total sample (n = 73). We then conducted a correlation matrix examining the relationship between the IVs, potential mediators, and viral load as the DV only among individuals on HAART (n = 47). As indicated above, there was insufficient variation in past four day nonadherence for all medications and HAART specifically to include these as DVs. See tables v and vi for the results of both correlation matrices.

From the results of the correlation matrices (tables v and vi), a variable was considered as a potential mediator if there was a significant association between one of the IVs and the potential mediator (*a* path), and the mediator(s) and the DV (*b* path), which included either 1) frequency of reasons endorsed for medication nonadherence for the total sample; or 2) viral load for individuals on HAART.

As indicated in table v, the only variables significantly related to frequency of reasons endorsed for medication nonadherence were HAMD and punishment (the RPI environmental suppressors subscale [lower scores = greater punishment], with greater depressive symptoms (r = .26, p = .03) and higher levels of punishment (r = -.39, p = .001) both related to greater frequency of reasons endorsed for medication nonadherence.

HAMD was also significantly related to frequency of reasons endorsed for medication nonadherence (r = .26, p = .03).

As indicated in table vi, neither depressive symptoms nor any potential mediators were significantly related to viral load. We also examined viral load categorically among individuals on HAART, comparing individuals based on detectable viral load status (VL ≤ 50). We tested any differences for all key study variables (IVs and potential mediators), and there were no significant differences between individuals with a detectable viral load vs. undetectable at $p < .05$ (see Table viii).

Based on the results of the correlation matrices (tables v and vi), the only potential indirect effect to test in further analyses was the role of punishment (environmental suppressors subscale of the RPI) in the relationship between clinician-rated depressive symptoms and frequency of reasons endorsed for medication nonadherence for all participants. Specifically, the *a* and *b* paths were statistically significant: clinician-rated depressive symptoms (HAMD) were significantly related to punishment (r = -.26, p = .03), and punishment was significantly related to total medication nonadherence (frequency of reasons endorsed; r = .39, p = .001). Additionally, although not necessarily a requirement for mediation (Hayes, 2009), the *c* path was also significant: HAMD was significantly related to frequency of reasons endorsed for nonadherence (r = .26, p = .03). Thus, we chose to test punishment as a potential mediator of the relationship between HAMD and frequency of reasons endorsed for medication nonadherence.

Testing Mediation

We tested the mediating role of punishment in the relationship between depressive symptoms and frequency of reasons endorsed for all medication nonadherence (aligning with originally proposed Aim 3) using two approaches. We first ran a series of linear regression analyses without covariates to test whether the four criteria set by Baron & Kenny (1986) were met. There was (1) a significant direct effect of the IV (HAMD) on the DV (frequency of reasons endorsed for medication nonadherence) (B = .72, t(61) = 2.05, p < .05); (2) a significant effect of the IV(HAMD) on the potential mediator (punishment) (B = -.36, t(68) = -2.19, p < .05); (3) a significant effect of the mediator (punishment) on the DV (frequency of reasons endorsed for medication nonadherence) (B = -.81, t(64) = -3.32, p < .001); and (4) the effect of the IV (HAMD) on the DV (frequency of reasons endorsed for medication nonadherence) after controlling for the mediator (punishment) was no longer significant (B = -.50, t(61) = 1.46, p = .15), but the effect of the mediator (punishment) remained significant in the model (B = -.76, t(61) = -.2.89, p < .01). See Figure ii for a depiction of these relationships.

We also utilized non-parametric bootstrapping to test for significance of the indirect effect, which has been demonstrated to be a valid and powerful method for testing indirect effects (MacKinnon et al., 2004; Shrout & Bolger, 2002; Williams & MacKinnon, 2008). It is recommended for small samples because there are no assumptions about the shape of the sampling distribution of the indirect effect, unlike the Sobel test that assumes the sampling distribution of the indirect effect is normal (Preacher & Hayes, 2004). In these analyses, the indirect effects are significant if the 95% bias-corrected or percentile-based confidence intervals (CIs) for the indirect effect do not

include 0 (Preacher & Hayes, 2004). We utilized both bias-corrected and percentile-based CIs to interpret the significance of indirect effects.

The analyses were based upon 5,000 bootstrapped samples (recommended by Hayes, 2009), and we used the INDIRECT SPSS Macro developed by Preacher & Hayes (2008). See table vii for the bias-corrected and percentile-based CIs and point estimate for the indirect effect. Because zero was not included in either of the 95% CIs, the indirect effect was determined to be significantly different from zero at $p < .05$ (two-tailed). Specifically, individuals who demonstrated higher levels of clinician-rated depressive symptoms were more likely to perceive punishment in their environment, and through higher levels of punishment, were more likely to endorse a greater frequency of reasons for medication nonadherence (see table vii).[2]

Finally, given that the current study was cross-sectional, we also ran the proposed mediation models switching the mediator and DV to demonstrate that the DV was not also mediating the relationship between the IV and proposed mediators (Preacher & Hayes, 2004). We tested this using 5,000 bootstrapped samples using the same Macro (Preacher & Hayes, 2008). Results indicated there was not a significant indirect effect of the DV according to both the percentile-based and bias-corrected 95% CIs [*I.E.* = -.11, *S.E.* = .09; percentile-based 95% CI: *LL* = -.31, *UL* = .03; bias-corrected *LL* = -.37, *UL* = .01]. In sum, because zero was included in both the percentile-based and bias-corrected 95% CI, this suggested that the DV (frequency of reasons endorsed for nonadherence) did not mediate the relationship between depression and punishment.

[2] We conducted these analyses with and without controlling for HAART status, and the results did not differ (in both analyses, the percentile-based and bias-corrected CIs did not include 0). Controlling for HAART status, the point estimate of the indirect effect based on 5,000 bootstrapped samples = .23, bias = .009; 95% percentile-based CI: .01-.61; 95% Bias-corrected CI: .02 - .67.

Given the potential bi-directionality of this relationship (i.e., improvements in adherence resulting in improvements in depressive symptoms), we also ran the proposed mediation models switching the IV and DV to demonstrate that punishment was not also mediating the relationship between nonadherence as the IV and depressive symptoms as the DV. We again tested this using the same procedure stated above (Preacher & Hayes, 2008). Results indicated that there was not a significant indirect effect of punishment when the IV and DV were switched according to both the percentile-based and bias-corrected 95% CIs [*I.E.* = .02, *S.E.* = .02; percentile-based 95% CI: *LL* = -.01, *UL* = .07; bias-corrected *LL* = -.01, *UL* = .08].

Exploratory Aim

As an exploratory aim we initially wanted to consider multiple mediators together in the same model; however, as indicated above, no other potential variables besides punishment were eligible for inclusion in a larger multiple mediator model based on their relationships with either IV or DV. As such, we could not test the exploratory aim.

Chapter 4: Discussion

The current study sought to improve our understanding of potential mechanisms underlying the impact of depression on medication nonadherence drawing from early behavioral models of depression (Ferster, 1973; Lewinsohn, 1974). We aimed to test the key components of these models, (1) goal-directed activation, (2) positive reinforcement, and (3) punishment in one's environment as potential mediators of the relationship between depressive symptoms and medication adherence. Given the significant focus on depression as a barrier to medication adherence in HIV (Gonzalez et al., 2011a) as well

as chronic health conditions more generally (DiMatteo et al., 2000), yet scarce research testing potential explanatory mechanisms of this relationship, findings have important implications for informing our understanding of a potential mechanism by which depression may impact adherence. This is directly in line with numerous recent reviews that have pointed to the critical need for studies to test mediators of this relationship (e.g., Gonzalez et al., 2011a).

The current study recruited low-income, HIV positive substance users who are at high risk for poor HIV outcomes (i.e., resulting from HAART nonadherence or not being on HAART; Chander et al., 2009). Indeed, we found that a substantial portion of our sample recruited was not taking HAART (35.62%), further supporting the notion that this is a sample at extremely high risk for poor HIV outcomes. Given that a high proportion of the sample was not taking HAART, in addition to assessing HAART adherence, we also assessed adherence to other daily medication regimens (i.e., psychotropic medications, cardiovascular medications, diabetes medications, anticonvulsants, and hormones), which has been suggested to be a strong predictor of HAART adherence and may be particularly important for improving HIV outcomes in this population (Cruess et al., 2012; Wagner, 2003).

We assessed adherence using self-reported missed doses during the past four days (for all medications and HAART specifically), as well as two measures of adherence that capture a wider time window: frequency of reasons endorsed for nonadherence more generally and viral load. Rates of self-reported adherence in the past four days were extremely high, reaching almost 100%; this may reflect typical inflation of self-reported adherence behavior when asked to report on missed doses directly (Kalichman et al.,

2009; Liu et al., 2001; Simoni et al., 2006) or actual high adherence rates common in the context of a controlled, substance abuse treatment setting (Hicks et al., 2007). In sum, the ceiling in rates of self-reported missed doses may be a reflection of either limitations of the assessment method, closely monitored medication schedules in a controlled setting, or the limited time window of four days. As an alternative, we utilized the two adherence measures that captured a greater time window (frequency of reasons endorsed for nonadherence and viral load).

There was indeed greater variability in the other two main adherence outcome variables (frequency of reasons endorsed for missed doses of all medications and viral load). As indicated above, there was not a timeframe specified in the measure of reasons for nonadherence, and as such, even participants who did not miss doses in the past four days may have indicated reasons for nonadherence, for instance prior to coming to substance abuse treatment. Additionally, participants may have endorsed reasons for nonadherence even if they did not report missed doses given a greater tendency to minimize nonadherence when asked to report on missed doses directly (Kalichman et al., 2009; Liu et al., 2001; Simoni et al., 2006). Regarding viral load, this clinical measure typically reflects adherence rates over the past approximate three months, and clearly given that it does not rely on patient self-report may have captured greater rates of nonadherence (Liu et al., 2001; Miller & Hays, 2000). Thus, to assess overall medication nonadherence we used the single DV of frequency of reasons endorsed for nonadherence, and for HAART adherence, we used viral load. The self-reported ratios of missed doses (for HAART and other medications) were removed from further analyses given the ceiling in rates of nonadherence. We tested the proposed mediators examining the two

DVs separately, as well as two measures of depressive symptoms: self-reported (BDI) and clinician-rated (HAMD).

Summary of Findings

Adherence to all medications: frequency of reasons endorsed for nonadherence

Regarding frequency of reasons endorsed for nonadherence to all medications, only clinician-rated depressive symptoms were related to nonadherence, such that greater clinician-rated depressive symptoms were related to greater frequency of reasons reported for nonadherence. Self-reported depressive symptoms were unrelated to frequency of reasons endorsed for nonadherence ($r = .12$, $p > .05$). The only proposed mediator related to frequency of reasons for nonadherence was punishment, such that a greater degree of punishment in one's environment was related to greater frequency of reported reasons for nonadherence. Both activation and reward derived from one's environment were unrelated to frequency of reasons endorsed for nonadherence.

As such, we only tested punishment as the mediator of the relationship between clinician-rated depressive symptoms and adherence. Testing this relationship using a series of linear regression analyses as well as non-parametric bootstrapping, punishment mediated the relationship between clinician-rated depressive symptoms and nonadherence. Specifically, individuals who demonstrated higher levels of clinician-rated depressive symptoms were more likely to perceive punishment in their environment, and through higher levels of punishment, were more likely to endorse reasons for medication nonadherence. It was an unexpected finding that punishment would be more strongly related to clinician-rated depressive symptoms as opposed to self-reported depressive

symptoms, particularly given the high correlation amongst depression-related self-reported measures typically. It will be important to replicate this finding and explore several possible reasons in future work, including the possibility that factors associated with experiencing punishment in one's environment may reflect deficits in particular skills (e.g., social skills) that are more accurately assessed using clinician observation as opposed to self-report.

Punishment mediating the relationship between clinician-rated depressive symptoms and frequency of reasons endorsed for nonadherence is in line with the theoretical framework of external locus of control of reinforcement, particularly as applied to health behavior (Wallston, Wallston, & DeVellis; 1978). This theoretical framework suggests that the degree to which individuals expect that a particular outcome is contingent on their own behavior or personal characteristics is strongly related to the likelihood of engaging in that behavior (Rotter, 1975). Individuals with an external locus of control perceive little control or agency over behavioral outcomes, and as such are much less likely to persist with behaviors that may be difficult in the short-term but may lead to more positive long-term consequences (Rotter, 1966). This notion of lacking control over one's environment and feeling more subject to negative consequences despite behavioral efforts suggests that punishment and external locus of control are closely linked constructs. Indeed, laboratory evidence suggests that uncontrollability in an environment (i.e., in line with an external locus of control) is strongly associated with greater perceived punishment, and in turn lower rates of responsive behavior (Hiroto, 1974). Individuals with an external locus of control are more likely to report punishing experiences and lack of control over adverse consequences even despite attempts at

healthy behavior (Rotter, 1966; Wallston et al., 1978). Although pinpointing causality or directionality in the relationship between punishment and external locus of control may be difficult or nearly impossible—a history of punishing or aversive consequences may lead to perceptions of lack of control over one's environment, or alternatively an external locus of control may contribute to greater perceptions of punishment—evidence does support a strong relationship and overlap between these constructs (Rotter, 1966; 1975).

As applied to health behavior specifically, an external locus of control has been strongly implicated in depression, in particular in relation to symptoms of depression related to avolition (Benassi et al., 1988), substance use (Newcomb & Harlow, 1986), and persistence with self-care across numerous chronic conditions, such as diabetes (Schlenk & Hart, 1984), hypertension (Stanton, 1987), as well as HIV/AIDS (Aversa & Kimberlin, 1996; Evans et al., 2000). Individuals with an external health locus of control are less likely to perceive direct benefits from healthy behavior, and rather are more likely to report aversive consequences as a result of attempting healthy behavior and a lack of control over managing their health condition (Wallston et al., 1978). Regarding HAART specifically, individuals with an external health locus of control may be less likely to perceive the benefits or rewards associated with HAART adherence (e.g., taking control over one's health), and rather may be more likely to report negative consequences when attempting to adhere (e.g., perceived stigma, side effects, etc.; Aversa & Kimberlin, 1996; Evans et al., 2000). In sum, individuals with an external locus of control are more likely to perceive a lack of control over their health and more likely to report aversive consequences in response to efforts to take control over their health.

In line with the locus of control framework, the current findings indicate that punishment may be very relevant to individuals endorsing more frequent reasons for medication nonadherence, and that punishment may be more important in explaining the relationship between depression and barriers to medication adherence than the other two main components of early behavioral theories of depression—levels of activation and reward in one's environment. Although it has been well-established that activation and reward in one's environment are strongly related to depression, it may be that these constructs are not as strongly related to medication nonadherence. Alternatively, it may also reflect the setting in which the current study was conducted, a controlled environment with very little variability or flexibility regarding one's schedule. There are also very few ways to obtain reinforcement from one's environment in this controlled setting. Both of these characteristics may have made activation and reinforcement in one's environment less relevant to medication adherence in the recruitment setting. It would be interesting in future work to recruit from a community setting or an outpatient center where individuals have greater control over their schedule and opportunities for obtaining reinforcement in a more natural environment. It may be that in a different setting with fewer restrictions on one's activity level and activity options that levels of activation and reinforcement in one's environment would be more strongly related to medication nonadherence. However, these interpretations are speculative and require further empirical attention.

Adherence to HAART: Viral load findings

Regarding the relationships tested only among individuals on HAART (i.e., using viral load as the DV), neither measure of depressive symptoms nor any potential mediator

were related to viral load. As such, no analyses were conducted to test mediators of the relationship between depressive symptoms and viral load. There are a few potential reasons why no variables assessed were related to viral load. These analyses were only conducted among individuals taking HAART in the current sample (n = 47) given that viral load is only an indicator of adherence among individuals on HAART. Doing so greatly reduced the sample size, and potentially meaningful relationships may not have been able to be detected in such a reduced sample size, as the necessary sample size to be sufficiently powered to detect mediation using bootstrapping with the current effect sizes is approximately 54 to 71 (Fritz & MacKinnon, 2007). There also may not have been sufficient variability in our measure of viral load (even following transformation) to detect meaningful differences.

Finally, it has been suggested that clinician-rated measures of depression may be stronger predictors of adherence than self-reported depressive symptoms, particularly for objective measures of adherence such as viral load (Gonzalez et al., 2011b). In line with this evidence, we would have expected HAMD scores to be related to viral load, although as stated previously the small sample size may have reduced the likelihood of detecting this effect. HAMD was significantly associated with actual viral load count prior to transformation (r = .31, p = .04), but was non-significant following the log10 transformation. Effect sizes indicate a small to moderate relationship between HAMD and log10viral load (r = .19; d = .35). Given previous evidence that clinician-rated measures may be stronger predictors of objective adherence measurement (Gonzalez et al., 2011b), it would be interesting in future work to replicate findings using more

objective measurements of the proposed mediators as well (i.e., using real-time objective assessments of activation) when testing this model using viral load as the primary DV.

Limitations

Findings must be interpreted in light of important study limitations. First and foremost, the study design was cross-sectional, which limits our ability to infer causality. Although the majority of studies to date still do test mediation using a cross-sectional design, there have been important advantages noted of using a longitudinal design to test for mediation (Maxwell & Cole, 2007). This point is particularly important given potential bi-directionality of this relationship. It has been suggested that improved physical well-being (i.e., through greater rates of adherence) may also influence depressive symptoms (Kagee, 2012). Successful adherence may also induce feelings of mastery and accomplishment, which as a result may reduce depressive symptoms (in line with behavioral theories of depression; Ferster, 1973; Lewinsohn, 1974). Although bi-directionality was not empirically supported in the current study (i.e., when we re-ran mediation analyses switching the IV and DV), it is indeed an important limitation of a cross-sectional design that must be noted. Given the preliminary stage of current work—that this is the first attempt to identify behavioral mediators of the relationship between depression and adherence—as well as the difficult to track nature of this population, we did feel that a cross-sectional design was most appropriate at this stage; however, future efforts to replicate these findings in a larger trial should consider incorporating long-term follow ups.

A second important limitation of the current study relates to the measurement of adherence. The design would have been strengthened with the use of an objective

measure of adherence for all medications, not only viral load. Although difficult in a controlled environment with little privacy, the use of electronic pill caps (for HAART as well as other medications) would have been a potentially more accurate, objective measure of adherence. However, there have also been limitations noted regarding electronic pill caps, including only being able to measure adherence to a single pill, inability to assess whether a pill was actually taken (vs. the bottle being opened), as well as noted patient burden of electronic pill caps (Liu et al., 2001). Lastly, electronic pill cap technology is very expensive and perhaps not appropriate at this stage of research and for the scope of this project. However, other potentially more objective assessments of adherence such as unannounced pill counts or pharmacy refills would have been useful, particularly prior to or following discharge from the controlled environment.

Relatedly, given the controlled environment, there were very high rates of self-reported adherence in the past four days. This did not allow us to use past four day adherence ratios (for missed doses of HAART or other medications) as originally intended for recent adherence, and in turn, we relied only on viral load and a broader assessment of frequency of reasons endorsed for nonadherence for all medications. Although viral load is a recommended objective assessment of adherence, it was limited to only the individuals on HAART, which represented a smaller subset of our total sample.

Additionally, although assessing reasons endorsed for nonadherence has been suggested to be an effective strategy to minimize social desirability biases and other inaccuracies of self-reported adherence (Simoni et al., 2006), there are some significant limitations of this measure. It is unclear whether a greater frequency of reasons endorsed

for nonadherence reflects actual missed doses. It may be that some individuals perceive greater barriers to adherence and report nonadherence across a range of reasons, whereas other individuals may consistently miss more doses but for a single reason. In this case, the measurement of frequency of reasons endorsed for nonadherence may not accurately reflect number of missed doses. Given the ceiling in rates of self-reported missed doses in the current study, we could not accurately assess whether missed doses correlated with frequency of reasons for nonadherence. However, even if we had more variability in the reporting of missed doses and could examine the correlation between frequency of reasons endorsed and missed doses, the noted limitations of assessing missed doses via self-report may have still precluded our ability to answer questions regarding the accuracy of this measure (Simoni et al., 2006). Viral load and frequency of reasons endorsed for nonadherence also were not significantly correlated among individuals on HAART (r = .20, p = .21); however, we did not assess frequency of reasons endorsed for nonadherence to HAART specifically—which we would hypothesize would be most closely related to viral load—and thus including other medication types in our assessment of reasons endorsed for nonadherence may explain its lack of correlation with viral load. Future studies must examine the accuracy of assessing reasons endorsed for nonadherence as a measure of missed doses by comparing it to objective measures of adherence. Despite these potential limitations of using reasons endorsed for nonadherence as a proxy for adherence behavior, the measure does provide rich clinical information about barriers to adherence that is not captured by reporting on missed doses or viral load, which has the potential to provide very useful clinical targets in future developments of this work.

Other limitations of this measure include the fact that we did not separate medication classes when assessing reasons endorsed for missed doses. Most importantly, we did not assess frequency of reasons endorsed for nonadherence to HAART specifically compared to other medications and instead examined reasons endorsed for nonadherence to all daily medications jointly. It is possible that reasons for missed doses differ across different medical conditions and medication types; however, the same holds true across classes of HAART given differing dosing instructions and side effect profiles. By assessing reasons for nonadherence across HAART and other medications for those not taking HAART, we run the risk of confounding non-equivalent measures of adherence; we would expect this confounding to further reduce the likelihood of establishing systematic relationships with other variables, yet we still identified meaningful relationships between depressive symptoms, punishment, and reasons endorsed for nonadherence.

Additionally, although in the current study we were interested in adherence to other medications to capture adherence behavior among individuals not on HAART, it is also very likely that adherence to these other forms of medication, particularly antidepressants, may have a direct effect on HAART adherence given reduced depressive symptoms following regular antidepressant use. For instance, Horberg et al. (2008) found that depressed individuals taking serotonin reuptake inhibitors (SSRIs) showed similar rates of HAART adherence as non-depressed individuals. This is consistent with other studies demonstrating that treating depression using antidepressants is associated with improved medication adherence (Walkup, Wei, Sambamoorthi, & Crystal, 2008). However, there has also been some evidence suggesting that HAART adherence and

antidepressant adherence are highly correlated behaviors, and it may not only be the *result* of antidepressant use that HAART adherence improves. For instance, one study showed that mean psychotropic medication adherence over a three-month period was significantly associated with greater HAART adherence over the same three-month period, and that it may not have been a consequence of the antidepressants that HAART adherence was related; rather, that the behaviors were highly correlated (Cruess et al., 2012). Thus, although there may be limitations in considering adherence to other forms of medication as a proxy for HAART adherence, there is also some evidence suggesting it may be an accurate indicator. Although ideally we would have been able to assess these questions in the current study, we were not able to for a few reasons, including no assessment of adherence to antidepressant medications alone, the ceiling in rates of past four day adherence ratios, as well as the cross-sectional design. Future work that follows participants over time and measures adherence to HAART following initiation or re-initiation of other medications, specifically antidepressants, would be necessary to address these limitations.

Another primary limitation of the current study related to recruitment criteria. Given that the majority of participants were recruited as part of a larger trial not primarily focused on medication adherence, not all participants were required to be on HAART. The design would have been significantly strengthened if all individuals recruited were on HAART, and ideally based on a certain threshold of HAART nonadherence as suggested by the CDC recommendations for assessing best practices in HIV medication adherence research (Charania, 2010). Yet, one could also argue that by recruiting individuals who were not on HAART, we were targeting the highest risk patients for poor

HIV/AIDS outcomes (CDC, 2011a). Additionally, given the extremely high rates of non-use and starting and stopping HAART among substance users, only including participants on HAART may have significantly limited our sample and may have reduced potential for generalizability to other samples. In sum, by recruiting all individuals and assessing adherence to other medications for individuals not on HAART, we were able to test our model using a very high risk sample that may be most representative of low-income, minority substance users living with HIV/AIDS. However, to test this model for HAART adherence specifically, future work should recruit based on specific parameters related to HAART use.

Finally, the current study only tested one specific mechanism according to a strictly behavioral theoretical framework; future work may consider testing more elaborate mediational models that incorporate other potential explanatory mechanisms, for instance cognitive and neurocognitive variables that are related to adherence to HAART and other forms of medication (Hinkin et al., 2004; Stilley, Sereika, Muldoon, Ryan, & Dunbar-Jacob, 2004). However, it is important to note that this focus on behavioral theories was an important consideration, as the most commonly endorsed reasons for nonadherence are behavioral (Palmer et al., 2003). Additionally, these behavioral variables align closely with the treatment targets of existing integrated interventions for addressing depression and adherence; as such, the current findings may be useful for spurring future efforts to continue to improve parsimony of these interventions (Daughters et al., 2010; Safren et al., 2012).

Implications and Future Directions

Despite the noted limitations of the current study, the findings are an important first step to test potential mediators of the relationship between depression and medication adherence and have important implications in improving our understanding of a potential mechanism by which depression may impact adherence. By pinpointing specific processes through with depression relates to adherence, we can develop targeted interventions and improve efficacy and parsimony of existing interventions. If findings continue to replicate, this may suggest adapting existing interventions for depression and adherence among substance users to focus more exclusively on reducing punishment in one's environment and the impact punishment may have on one's perceived self-efficacy to adhere to medication regimens. For instance, cognitive behavioral interventions have been developed to simultaneously target depressive symptoms and improve medication adherence among substance users with HIV/AIDS (Daughters et al., 2010; Safren et al., 2012); these interventions target punishment to some degree (i.e., psycho-education regarding one's control over their health condition through self-care and HAART adherence), and perhaps findings support the notion that these interventions should more directly target perceptions or experiences of punishment that may interfere with adherence. Additionally, findings may also inform screening tools, such that individuals reporting greater levels of punishment may be identified and enrolled in targeted interventions to prevent future nonadherence. Prevention interventions focusing on punishment may similarly incorporate psycho-education regarding the control individuals have over their health condition through adherence, as well as openly discussing potential negative consequences of HAART use (i.e., side effects, stigma, etc.) so that the potential

punishing experiences one may encounter when taking HAART can be anticipated and normalized.

In sum, findings support the need for targeting perceptions of punishment as a potential means to improve medication adherence, yet future research is necessary to address existing study limitations. Future studies should incorporate larger sample sizes, longitudinal designs, more objective measures of medication adherence, and recruit in an outpatient or non-treatment seeking sample based on HAART use. Future work may also consider other potential mediators and contrast indirect effects to test whether punishment does indeed explain this relationship over and above other relevant factors. Despite the limitations, current findings are important in improving our understanding of a potential mechanism by which depression may impact medication adherence. Additionally, focusing on adherence behaviors even among HIV-infected individuals not on HAART addresses the needs of a group most at risk for poor HIV/AIDS outcomes. These findings represent a first step in improving our understanding of how depression may relate to medication nonadherence among HIV-infected substance users at high risk for poor health outcomes. It is the hope that these findings will spur efforts for continued refinement of clinical interventions for this group.

Tables

Table i

Demographic information and Axis I and II psychopathology for total sample and comparing groups based on HAART status.

	Overall (n = 73)	On HAART (n = 47)	Not on HAART (n = 26)	Statistic	p value
Demographics					
Age, mean (SD)	45.1 (7.8)	45.8 (7.9)	45.0 (8.8)	$t(71) = 0.40$	.69
Gender				$\chi^2(2) = 3.06$	.22
Male, %	41.1	45.7	26.9		
Female, %	50.7	47.8	61.5		
Transgender, %	8.2	6.5	11.5		
Marital Status				$\chi^2(2) = 1.22$	.54
Single, %	62.7	58.7	73.1		
Separated/divorced, %	26.7	30.4	19.2		
Married, %	9.3	10.9	7.7		
Race/ethnicity				$\chi^2(3) = 3.48$	.32
White, %	1.3	2.1	0.0		
Black, %	94.5	93.6	96.4		
Hispanic , %	2.7	4.3	0.0		
Native American, %	1.4	0.0	3.6		
Heterosexual, %	71.2	73.9	71.4	$\chi^2(2) = 0.09$	.96
≤ High school/GED, %	78.7	78.7	78.6	$\chi^2(1) = 0.00$	.99
Total Annual Income <$10,000, %	78.7	80.9	75.0	$\chi^2(1) = 0.36$	.55
Unemployed, %	89.3	85.1	96.4	$\chi^2(1) = 2.36$	.12
Psychopathology*					
Current MDD, %	17.8	15.9	23,1	$\chi^2(1) = 0.56$	.46
Lifetime MDD, %	45.2	51.1	28.6	$\chi^2(1) = 1.25$	.26
Bipolar I, %	15.1	11.1	23.1	$\chi^2(1) = 1.80$	.18
Lifetime PTSD, %	19.2	20.0	22.2	$\chi^2(1) = 0.02$	.96
Crack/cocaine dependence (past year), %	54.8	48.9	60.7	$\chi^2(1) = 1.81$	.18
Alcohol dependence (past year), %	32.9	30.4	35.7	$\chi^2(1) = 0.69$	.41
Opioid (heroin) dependence (past year), %	24.7	24.4	25.0	$\chi^2(1) = 0.03$	.86
ASPD	27.8	28.9	28.0	$\chi^2(1) = 0.01$	.94

*All Axis I and II diagnoses with ≥15% prevalence in current sample are listed. MDD = Major Depressive Disorder. PTSD = Posttraumatic Stress Disorder. ASPD = Antisocial Personality Disorder

Table ii

Health status and health care-related factors for total sample and by HAART status.

	Overall (n = 73)	On HAART (n = 47)	Not on HAART (n = 26)	Statistic	p value
Health Status					
CD4 Count, mean (SD)	448.46 (247.11)	431.00 (248.37)	492.11 (245.39)	$t(61) = -.89$	.38
Years since HIV diagnosis, mean (SD)	10.88 (10.75)	10.74 (6.99)	11.26 (9.24)	$t(61) = -.23$	.82
SF-36 (PCS)	58.77(10.75)	59.25 (11.05)	57.91 (10.36)	$t(70) = .51$	.61
SF-36 (MCS)	59.79 (13.13)	59.87 (11.16)	59.66 (16.23)	$t(70) = .06$	.95
Health Care-Related Factors					
Has a PCP, %	97.26	97.87	96.15	$\chi 2$ (1) = .17	.60
Has a health insurance plan, %	95.89	95.74	96.15	$\chi 2$ (1) = .01	.71

PCS = SF-36 Physical Component Summary Scale; MCS = SF-36 Mental Health Component Summary Scale; PCP = Primary Care Physician

Table iii

Levels of IV (depressive symptoms), mediators (goal-directed activation and reinforcement/punishment), and DV (medication adherence, viral load) for total sample and by HAART status.

	Overall (n = 73)	On HAART (n = 47)	Not on HAART (n = 26)	Statistic	p value
Depressive symptoms					
BDI-II	13.54 (11.00)	13.49 (11.70)	13.62 (9.89)	$t(69) = -.05$	.96
HAMD	2.99 (3.32)	2.86 (3.45)	3.20 (3.12)	$t(67) = -.40$	.69
Mediators					
BADS-AC	23.08 (10.27)	21.48 (10.79)	25.92 (8.77)	$t(70) = -1.79$	.08
BADS-AR	23.22 (12.46)	23.74 (12.19)	22.31 (13.13)	$t(70) = .47$	.64
BADS-WS	20.03 (7.52)	22.13 (7.59)	21.85 (7.52)	$t(70) = .15$	.88
BADS-SI	20.03 (7.48)	20.22 (7.92)	19.69 (6.76)	$t(70) = .28$	.78
BADS-Tot	88.36 (25.92)	87.57 (27.22)	89.77 (23.90)	$t(70) = -.34$	.73
RPI-Reward	34.29 (6.10)	34.11 (6.51)	34.62 (5.42)	$t(70) = -.34$	.74
RPI-Punish	21.46 (4.57)	21.57 (3.99)	21.27 (5.53)	$t(70) = .26$	.79
RPI-Tot	55.75 (8.27)	55.67 (7.67)	55.88 (6.29)	$t(70) = -.10$	.92
Medication Adherence					
ACTG-reasons	11.97 (9.42)	12.37 (9.39)	11.18 (9.67)	$t(63) = .48$	.63
Log10VL	2.42 (1.08)	1.98 (.83)	3.50 (.84)	$t(63) = -6.56$	.001

BADS-AC = Behavioral Activation for Depression Scale, Activation Subscale; BADS-AR = Avoidance/Rumination Subscale; BADS-WS = Work/School Impairment Subscale; BADS-SI = Social Impairment Subscale; BADS-tot = Total Score; RPI-Reward = Reward Probability Index, Reward Probability Subscale; RPI-Punishment = Environmental Suppressors Subscale; RPI-Total = Total Score; ACTG-reasons = total frequency of reasons endorsed for nonadherence using the AIDS Clinical Trials Group Questionnaire; Log10VL = viral load count log10 transformed

Table iv

Relationship between potential covariates and both dependent variables.

	Frequency of reasons for nonadherence: Total sample (n = 73)		Viral load (log10 transformed): Individuals on HAART (n = 47)	
	Statistic	p value	Statistic	p value
Demographics				
Age, mean (SD)	r = -.07	.56	r = .03	.85
Gender	$F(2, 65) = 1.55$	.22	$F(1, 43) = .46$	.50
Marital Status	$F(4, 63) = .43$	.78	$F(4, 40) = 2.32$	.07
Race/ethnicity	$F(3, 64) = 1.03$	.39	$F(2, 42) = .42$	.66
≤ High school/GED, %	$F(1, 66) = .14$	.71	$F(1, 43) = .02$	.88
Total Annual Income <$10,000, %	$F(1, 66) = .03$	.86	$F(1, 43) = .33$	.57
Unemployed, %	$F(1, 66) = .65$	.42	$F(1, 43) = .30$	.59
Health Status				
CD4 Count	r = -.14	.28	r = .32	.03
Years since HIV diagnosis	r = .10	.47	r = -.10	.53
SF-36 (PCS)	r = .10	.43	r = -.18	.24
SF-36 (MCS)	r = -.21	.10	r = -.06	.68

Table v

Correlation matrix of depressive symptoms, potential mediators, and medication adherence (self-reported reasons for all medications missed) for all participants (n = 73).

	1	2	3	4	5	6	7	8	9	10	11
1. BDI-II	--	.52***	-.08	-.37***	-.45***	-.38***	-.46***	-.36**	-.22	-.39***	.12
2. HAMD		--	-.14	-.26*	-.35**	-.19	-.34**	-.31**	-.26*	-.38**	.26*
3. BADS-AC			--	-.07	.09	.03	.40***	.34**	.23	.38***	-.03
4. BADS-AR				--	.56***	.68***	.81***	.16	.38***	.33**	-.16
5. BADS-WS					--	.60***	.77***	.40***	.37**	.50***	-.18
6. BADS-SI						--	.80***	.34**	.38***	.46***	-.24
7. BADS-Tot							--	.42***	.49***	.59***	-.21
8. RPI-Reward								--	.17	.84***	-.15
9. RPI-Punish									--	.68***	-.39***
10. RPI-Tot										--	-.32*
11. ACTG reasons											--

***$p < .001$; ** $p < .01$, * $p < .05$

Table vi

Correlation matrix of depressive symptoms, potential mediators, and viral load for participants on HAART (n = 47).

	1	2	3	4	5	6	7	8	9	10	11
1. BDI-II	--	.45***	-.07	-.47***	-.48***	-.50***	-.52***	-.40**	-.30*	-.49***	.08
2. HAMD		--	-.07	-.30	-.32*	-.20	-.31*	-.33*	-.24	-.41**	.20
3. BADS-AC			--	.03	.11	.15	.48***	.26	.30*	.37*	.06
4. BADS-AR				--	.57***	.65***	.81***	.25	.44**	.43**	-.07
5. BADS-WS					--	.60***	.75***	.43**	.30*	.52***	-.26
6. BADS-SI						--	.81***	.48***	.41**	.62***	-.20
7. BADS-Tot							--	.47***	.52***	.67***	-.14
8. RPI-Reward								--	.01	.85***	-.09
9. RPI-Punish									--	.53***	.16
10. RPI-Tot										--	.01
11. log10VL											--

***$p < .001$; ** $p < .01$, * $p < .05$

Table vii

Testing the indirect effect of punishment based on 5,000 bootstrapped samples.

Indirect effect	*Boot*	*Bias*	*SE*
Punishment	.23	.009	.15
Percentile-Based 95% CI	*LL*	*UL*	
Punishment	.01	.59	
Bias-Corrected 95% CI	*LL*	*UL*	
Punishment	.03	.64	

IV = HAMD; DV = Frequency of reasons endorsed for medication nonadherence using ACTG; Mediator = RPI Environmental Suppressors Scale.

Table viii

Comparing individuals on HAART based on detectable viral load status: examining differences in depression and potential mediators.

	VL ≤ 50 (*n* = 21)	VL > 50 (*n* = 24)		
	Mean (SD)	Mean (SD)	Statistic	*p* value
BDI-II	11.62 (10.92)	15.48 (12.48)	*t*(42) = -1.09	.28
HAMD	2.85 (3.66)	3.00 (3.37)	*t*(41) = -.14	.89
BADS-AC	21.05 (11.89)	22.25 (10.01)	*t*(43) = -.37	.72
BADS-AR	25.62 (12.75)	21.33 (11.20)	*t*(43) = 1.20	.24
BADS-WS	23.52 (6.66)	20.72 (8.42)	*t*(43) = 1.14	.26
BADS-SI	21.81 (7.64)	18.67 (8.16)	*t*(43) = 1.33	.19
BADS-Tot	92.00 (28.97)	83.17 (25.98)	*t*(43) = 1.08	.29
RPI-Reward	34.71 (7.39)	33.54 (5.89)	*t*(43) = .59	.56
RPI-Punish	21.05 (4.42)	21.96 (3.69)	*t*(43) = -.75	.45
RPI-Tot	55.76 (8.10)	55.50 (7.60)	*t*(43) = .11	.91

Figures

Figure i

Conceptual Model of Study Aims

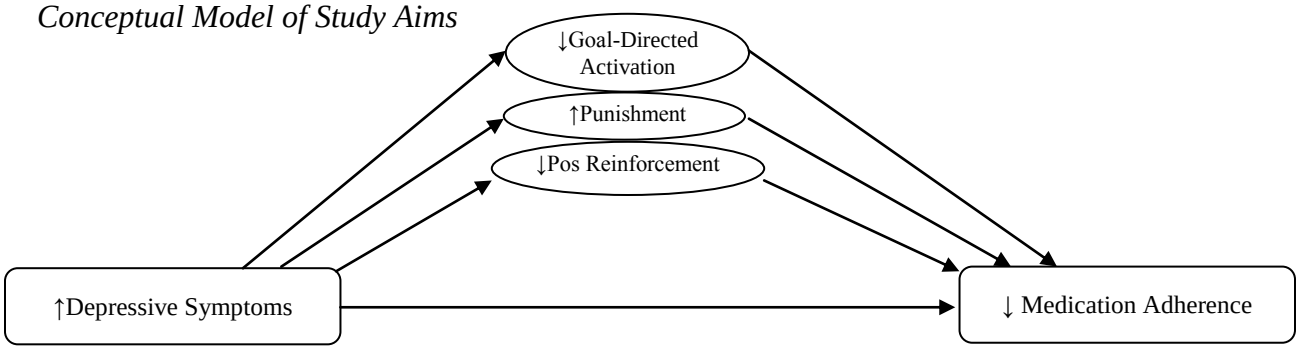
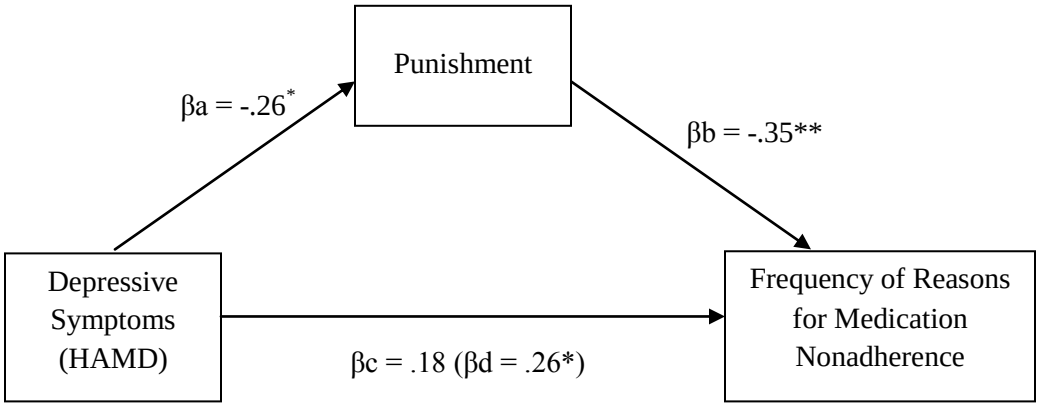


Figure ii

Causal steps linear regression results of the mediating role of punishment.



Note. * $p < .05$ ** $p < .01$, *** $p < .001$

βa = standardized beta coefficient of the IV -> the mediator; βb = standardized beta coefficient for the mediator -> DV with IV in the model
βc = standardized beta coefficient for the IV with mediator in the model; βd = standardized beta coefficient for the IV without the mediator in the model

Appendix

Daily Activities and HIV Medication Adherence

A series of studies have examined the impact of "daily routinization," defined as the extent to which one's daily life is structured, in relation to HIV medication adherence. Ryan & Wagner (2003) first conducted an exploratory, qualitative study in which they interviewed 27 HIV positive individuals with drug abuse histories (past or current) to examine circumstances surrounding missed doses (54% of the sample consisted of active drug users, and 36% had clinical depression). The study focused on "episodic" rather than "global" adherence patterns (focusing on specific times an individual misses) to have a more in-depth understanding of factors influence nonadherence patterns. The primary themes that emerged across all interviews were the extent to which participants "routinized" their pill regimen and the specific factors that influenced routinization. Their conclusions suggest that the degree of structure in one's environment and factors associated with ability to maintain these routines play an important role in successful adherence.

However, their study also identified that "hectic days filled with errands, chores" could also be associated with nonadherence due to exhaustion. "Being out, whether running errands, visiting friends, going to meetings or appointments" were associated with missing doses, and the activities may act as a "double-edged sword" providing structure and stability, yet also increasing fatigue and chaos associated with nonadherence. A salient quote from their interviews well-captures the issue: "too many things and I forget the most important thing—my medications." Many individuals felt that pill-taking was something that needed to not only be tied to specific daily activities,

but also “an even bigger and more important goal,” “a person has to make up their mind about what is important to them.”

Regarding substance use, their findings suggested that substance use and nonadherence were not always directly correlated; rather, there was often a more indirect or delayed effect of substance use on the environment that was associated with nonadherence, rather than being a direct cause of missed doses. Findings indicated that it was difficult to attribute missed doses to a specific incident of drug use, but rather more about how drug use is tied into and affects daily routine through environmental and behavioral pattern disruptions. This study offered great insight into this key behavioral factor influencing adherence; yet, authors acknowledge a key barrier in moving forward to a quantitative, empirical investigation of this relationship: “no established methods for reliably assessing routinization” (Ryan & Wagner, 2003).

As such, as a follow up study to this initial qualitative study, Wagner & Ryan (2004) conducted a quantitative study aiming to further investigate the relationship between routinization of daily behaviors and activities in relation to adherence among HIV-positive drug users and to develop an assessment measure of the construct of routinization. The assessment they developed of routinization of daily activities examined specific categories of activities, and participants reported how often they engaged in each of 14 behaviors related to meals, responsibilities (work, errands, appointments), socializing (visit friends inside or outside house, attend meetings/support groups), watching a favorite TV program, and staying overnight in other locations. Authors also utilized a more generalized 9-item measure of the degree of structure and organization in daily life (example item includes “my days consist of doing the same things at the same

time") that had been developed by their team in previous research (Wagner, Remien, Deloezal, & Carballo-Dieguez, 2002). They recruited 51 participants with a history of drug dependency (past or current). The sample was 90% male, racially diverse (33% White, 43% Black), 22% were employed, 47% had some college, and 65% had stable housing. Regarding substance use, 47% had used illicit drugs in the past month, 39% had a current drug dependency, and regarding depression, 25% met criteria for a depressive mood disorder.

Their findings demonstrated that a high frequency of four daily activities: eating breakfast, watching a favorite television program, attending meetings, and sleeping at home were significantly associated with high levels of adherence. A lower frequency of having friends over to visit was associated with higher adherence. A composite score that took into account how much a patient's daily routine incorporated these specific behaviors was significantly associated with adherence (r = .63). In a final regression model, daily routinization predicted over and above all other independent variables associated with adherence (gender, diagnostic status (drug dependency and depression), patient-provider relationship, and perceived treatment efficacy) and accounted for 36% of the variance in predicting adherence. None of the other variables independently associated with adherence were significant predictors of adherence in the larger model, demonstrating that routinization of daily activities predicted nonadherence over and above even levels of depression and substance use.

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