

ABSTRACT

Title of Thesis: THE RELATION BETWEEN SUBSTANCE
USE AND MEDICATION ADHERENCE
AMONG HIV POSITIVE SUBSTANCE
USERS IN RESIDENTIAL TREATMENT

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Poor medication adherence is problematic among HIV positive, low-income African-American substance users. Substance use has been shown to be associated with poor medication adherence, though we do not know the mechanism that underlies this relationship. Lack of positive environmental rewards and the propensity to discount delayed rewards may be possible mechanisms to explain this relationship. Using baseline data from a randomized controlled trial, we examined the relationships between substance use and medication adherence, testing both environmental rewards and delay discounting as independent mediators. There was a main effect of substance use on adherence, such that high frequency of substance use predicted poor adherence. There was also a main effect of environmental rewards on adherence, such that a lack of environmental reinforcement predicted poor adherence. This study shed light on the processes

that contribute to low adherence, namely substance use and lack of environmental contingencies, and suggests important targets for intervention.

THE RELATION BETWEEN SUBSTANCE USE AND MEDICATION ADHERENCE
AMONG HIV POSITIVE SUBSTANCE USERS IN RESIDENTIAL TREATMENT

by

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Table of Contents

Table of Contents	ii
List of Tables	iii
List of Figures	vi
Section 1: Introduction	1
Adherence to HAART	1
Substance use and medication adherence	2
Research on mechanisms	3
Theoretical framework for the relationship between substance use and HAART adherence	4
Lack of positive reinforcement in the environment	5
Propensity to discount delayed rewards	6
Current Study	7
Primary aims and hypotheses	8
Exploratory aims	9
Section 2: Methods	9
Participants	9
Measures	10
Data analysis	13
Section 3: Results	15
Participants	15
Hypothesis Tests	15
Section 4: Discussion	18
Discussion	18
Limitations and future directions	22
Bibliography	26

Bi-variate correlations and descriptive statistics for key study variables

	ACTG Reasons	Past Year Substance Use	RPI total	Large K values	Medium K values	Small K values	CD4 Count	Viral Load
ACTG Reasons	1	.251*	-.357**	.033	-.102	-.030	-.072	.127
Past Year Substance Use		1	.129	-.004	.063	-.057	-.162	-.004
RPI total			1	.125	.153	.037	-.077	.091
Large K values				1	.809**	.695**	.064	-.157
Medium K values					1	.817**	-.010	-.156
Small K values						1	.004	-.104
CD4 Count							1	-.129
Viral Load								1
<u>HAART</u>								
Mean	11.76	7	55.10	.0499	.0583	.0786	455.34	4462.02
SD	8.65	4.6	8.01	.0729	.0806	.0798	248.84	21495.86
Minimum	0	0	40	.000251	.000632	.000160	17	20
Maximum	31	20	74	.248848	.250000	.250000	1033	128000
<u>Not on HAART</u>								
Mean	11.34	9.2	56.06	.0286	.0377	.0472	413.63	38667
SD	9.2	3.79	9.02	.0498	.0549	.0536	29.46	69592.76
Minimum	0	0	33	.000158	.000160	.000160	8	300
Maximum	36	17	77	.248848	.250000	.159085	810	242320

Table 1.

Means, Standard deviations, and bi-variate correlations of key study variables

*Correlation is significant at $p < 0.05$

**Correlation is significant at $p < 0.01$

Substance Use Frequencies (entire sample)

	Alcohol	Cocaine	Marijuana	Opioid
Never	20%	25.3%	54.9%	72.6%
One time	1.3%	6.7%	7.0%	4.1%
Monthly or less	12%	5.3%	15.5%	2.7%
2-4 times/month	13.3%	5.3%	7.0%	0%
2-3 times/week	13.3%	20%	1.4%	4.1%
4 or more times/week	40%	37.3%	14.1%	16.4%

Table 2.

Percentage of participants using each drug at various frequencies in the last year

Substance Use Correlations

	Alcohol	Cocaine	Marijuana	Opioid
Alcohol	1	.393**	.162	-.042
Cocaine		1	-.042	.062
Marijuana			1	-.101
Opioid				1

Table 3.

Bi-variate correlations between past year Alcohol, Marijuana, Cocaine, and Opioid Use

*Correlation is significant at $p < 0.05$

**Correlation is significant at $p < 0.01$

Final Model for the Relation between Substance Use and Self-Reported Adherence

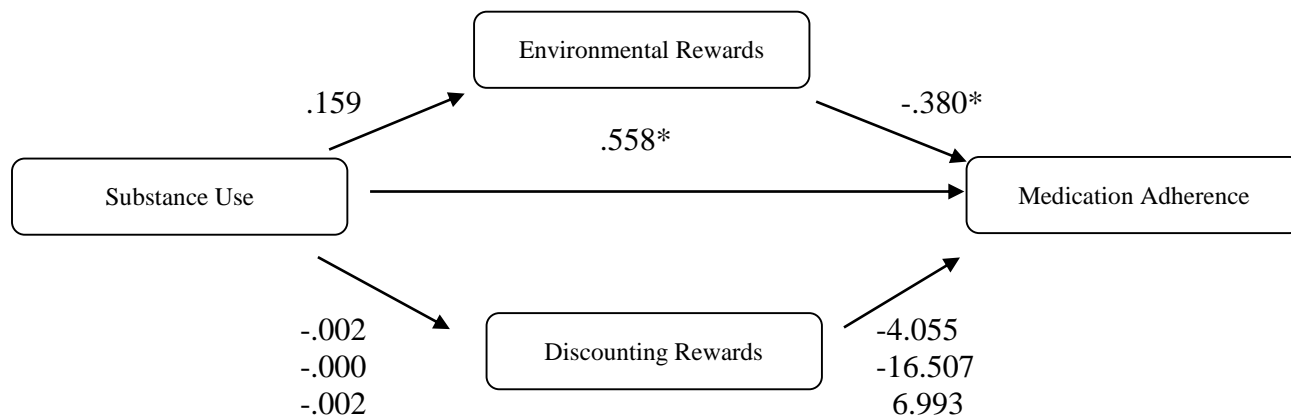


Figure 1.

Unstandardized estimates for the relation between substance use, environmental rewards, delay discounting, and medication adherence (* $p < 0.05$)

Introduction

Adherence to Highly Active Antiretroviral Therapy (HAART)

An estimated 1.1 million people in the United States are living with HIV (CDC, 2012). In the era of highly active antiretroviral therapy (HAART), morbidity and mortality as a result of HIV/AIDS has been declining (Crum et al., 2006). However, for HAART to be effective in controlling the progression of HIV/AIDS, adherence to a strict medication regimen must be near perfect (Shuter, Sarlo, Kanmaz, Rode, & Zingman, 2007). Despite the importance of near perfect adherence for disease management, actual rates of HAART adherence are low, ranging from 4-30% (Paterson, Swindells, Mohr, Brester, Vergis, Squier, C., et al., 2000; Golin, Liu, Hays, Miller, Beck, Ickovics, Kaplan, & Wenger, 2002). There are significant public health implications for low adherence in general, but the negative consequences of low adherence are especially prominent among groups that show disparities in terms of higher incidence of HIV/AIDS, such as low-income African-Americans (CDC, 2011; Kuo, Greenberg, Magnus, Phillips, Rawls, Peterson, et al., 2011; DC Department of Health, 2010, Golin, et al., 2002).

Across chronic health conditions, medication adherence is imperative for improving health outcomes, which is particularly relevant for individuals living with HIV, as there are often medical comorbidities in this population that require strict adherence to medication (Altice, Kamarulzaman, Soriano, Schechter, & Friedland, 2010). Near perfect adherence to HAART is necessary for viral suppression (Bangsberg et al., 2001; Bangsberg et al., 2006), and nonadherence and inconsistent adherence is related to a greater likelihood of producing strands of HIV that are of medication-resistant, additional health complications, and increased morbidity and mortality (Garcia de Olalla, Knobel, Carmona, Guelar, Lopez-Colomes, & Cayla, 2002). Due to the important individual health consequences and larger public health implications of

non-adherence or low adherence to various medications in this population, it is imperative to study the factors that contribute to these low rates of adherence for substance users.

Substance use and medication adherence

One well-researched factor that contributes to low medication adherence in general among HIV positive individuals is substance use. This relationship is particularly important because the incidence of substance use among HIV infected individuals in the U.S. is high, with estimates of HIV and co-occurring substance use ranging from 40-74% (Bing et al, 2001; McGowan, Weinstein, Samenow, Stinnette, Barkanic, Rebeiro, & Hulgán, 2011; Skeer, Mimiaga, Mayer, O’Cleirigh, Covahey, & Safren, 2012). Regarding HIV medication specifically, numerous studies have found support for the relation between substance use and poor HAART adherence across different drug classes. For example, Arnsten and colleagues (2002) examined drug use as a predictor of HAART adherence among past or current opioid users who have HIV, and found cocaine use to be among the strongest predictors of low HAART adherence as measured by an electronic cap (MEMS cap; Arnsten, Demas, Grant, Gourevitch, Farzadegan....& Schoenbaum (2002). Additionally, Stein and colleagues (2000) found ongoing drug use to be significantly associated with decreased HAART adherence in a sample of outpatient methadone users. Hinkin and colleagues found that substance abuse was associated with sub-optimal adherence in a sample of outpatients seeking HIV care (Hinkin, Hardy, Mason, Castellon, Durvasula, Lam, & Stefaniak, M., 2004). Moreover, in a review of 41 studies of adherence to HAART among substance users, Malta and colleagues (2008) found that active substance use was associated with poorer adherence overall. Additionally, a review by Gonzalez and colleagues (2011) summarized the extant literature regarding the impact of substance use on HIV medical treatment, and concluded that substance use significantly impacts effective disease

management for people living with HIV/AIDS (PLWHA) due to low rates of medication adherence.

In addition to the correlation between substance use and low adherence, HIV positive substance users experience unique barriers to medication adherence. For example, a study of injection drug users living with HIV/AIDS found individual barriers to adherence (i.e. low positive attitude about HAART benefits, limited medical coverage, current drug use), suggesting that there are factors within the context of HIV positive substance users that warrant examination (Knowlton, A. R., Arnsten, J. H., Eldred, L. J., Wilkinson, J. D., Shade, S. B., Bohnert, A. S., ... & Purcell, D. W. (2010). The literature suggests a strong relation between substance use and medication adherence among PLWHA. Despite the relation between these constructs, we have a limited understanding of the mechanisms that underlie this relationship, and the extant literature has yet to elucidate why substance use is related to poor adherence among HIV positive substance users.

Research on mechanisms

Improving our understanding of the relation between substance use and low adherence may serve to inform targeted interventions. Although there is evidence to support the relation between substance use and adherence, little is known about potential mechanisms that underlie this relationship (Arnsten et al, 2002; Peretti-Watel et al, 2006; Golin et al, 2002; Hinkin et al., 2007). Behavioral reasons (e.g. avoiding medication due to unpleasant side effects and complexity of medication regimen) are the most common factor underlying missed medication doses, highlighting the importance of studying behavioral mediators (Chesney, 2003). It has been shown that engaging in substance use treatment (especially substitution therapy) is a protective factor against low adherence among HIV positive substance users, perhaps due to engagement in

structured daily routines (Malta et al., 2008). Thus, this suggests that behavioral treatment for substance use might have a positive impact on adherence. Many investigators call for integration of substance use treatment and treatments for adherence (Safren et al., 2009; Tucker et al., 2004; Hinkin et al., 2007), and there are behavioral treatments developed based on behavioral theories that aim to decrease substance use and increase adherence (Daughters et al., 2010). Though there is evidence to support the efficaciousness of these behavioral treatments, the mechanisms that underlie their success is unknown. This focus on behavioral treatments boosts the argument to investigate behavioral mechanisms in order to develop targeted treatments.

Theoretical framework for the relationship between substance use and low adherence

In an effort to understand mechanisms underlying the relationship between substance users and poor adherence, it is useful to begin with a clear theoretical framework. A behavioral perspective (Skinner, 1953; Bandura and Walters, 1963; Bandura, 1969) might be particularly useful when conceptualizing this relationship. It is well documented that substance use is developed and maintained as a result of a lack of alternative, substance-free reinforcement in the environment (Carroll, 1996; Higgins, Heil, & Lussier, 2004; Daughters et al., 2008). If substance users experience a lack of positive reinforcement from the environment, they may place less value on a healthy lifestyle, which includes adhering to a complex medication regimen. Furthermore, the principles that underlie substance use maintenance are indeed similar to those that underlie medication nonadherence; specifically the reinforcers for substance use behaviors or nonadherence behaviors are immediate, and the reinforcers for the opposite behaviors (abstinence from drug use; adherence to a medication) regimen are delayed. Using this as a framework for conceptualizing the relationship between substance use and low adherence among PLWHA, potential mechanisms can be identified to explain this relationship.

Lack of positive reinforcement in the environment

One potential mechanism in the relationship between substance use and poor adherence based in basic behavioral theory is a lack of access to rewards from non-substance related activities that occur in the environment. If substance users are experiencing a lack of positive reinforcement from the environment for non-substance using activities because they are not accessing rewards from living a healthy and active life, with substance use being the primary source of reward, they may be less inclined to take their medication as prescribed given its role in achieving a healthy life. The association between substance use and lack of access to environmental contingencies is well documented (Correia et al., 2005; Van Etten et al., 1998; Murphy et al., 2005), though questions remain regarding directionality.

There is some evidence that substance use directly impacts an individuals' lack of access to non-substance based environmental contingencies. Substance users reliably rate reinforcement from non-substance using activities as less reinforcing than controls (Correia et al., 2005; Van Etten et al. 1998). In a study examining environment based contingencies among cocaine-dependent individuals, individuals who were abstinent from cocaine for 24 hours increased the frequency of engagement in non-substance using activities (Van Etten et al. 1998). In a longitudinal study of 18-22 year olds, lack of alternative reinforcers in the environment predicted cigarette smoking over a four-year period (Audrain-McGovern et al. 2011). Additionally, a prospective study investigating adults with heroin dependence found that ratings of non-substance stimuli negatively predicted future heroin use (Lubman et al. 2009). The link between these processes is likely bidirectional in that lack of access to environmental contingencies is a risk factor for the development of substance use, and once an individual is addicted, they do not

access (and subsequently do not receive positive reinforcement from) non-drug related activities in the environment.

Although the relationship between lack of positive reinforcement from the environment and adherence among HIV+ substance users has not been examined, there is evidence that positive reinforcement may be important in these self-care behaviors because the direct effects of medication alone is not sufficient to promote continued and accurate adherence. Thus, individuals who exhibit low adherence or non-adherence may require additional reinforcement from the environment in order to engage in self-care behaviors (Chesney, 2003; Chesney et al., 2000).

Propensity to discount delayed rewards

In addition to lack of positive reinforcement from the environment, there are other characteristics of a reinforcer that may be important for understanding why substance users have poor adherence. For example, one characteristic is the timing of the reinforcer. Thus, another mechanism in the relationship between substance use and poor adherence based in reinforcement theory is the propensity to discount a reward based on its delay. Delay discounting involves discounting the value of delayed rewards in favor of more immediate rewards (Bickel & Marsch, 2001). From the perspective of delayed reward discounting, because some of the unpleasant consequences of taking daily medication are often immediate (i.e. side effects, reminder of HIV status, medication regimen complications), it may be easy to choose the immediate reward of avoidance, so as not to experience such unpleasantness. This value of immediate rewards results in a discounting of delayed rewards, mainly improved health outcomes such as lower viral load and increased longevity. Indeed, one of the most established reasons why people do not take their medication is due to immediate unpleasant side effects (Ammassari et al, 2002; Chesney,

2000; Fogarty et al, 2002). The side effects may operate as a negative stimulus and thus may result in choosing the immediate reward of avoidance behavior (i.e., not taking the medication as prescribed) in order to avoid the potentially punishing aspects of these side effect profiles. This results in non-adherence to medication, despite the large but delayed potential positive outcomes of adherence (decreased viral load and lower risk of mortality). Substance use might be related to poor adherence because substance users discount the value of delayed rewards in favor of immediate rewards, and this propensity contributes to low adherence based on the timing of the reward (discounting delayed reward of healthy medication adherence in favor of immediate rewards of avoidance).

The link between substance use and the propensity to value immediate rewards over delayed, uncertain ones is well-established (Madden et al., 1997; Mitchell, 1999; Vuchinich & Simpson, 1998; Kirby & Petry, 2004; Yi et al., 2008). There is a wealth of literature to suggest substance users discount delayed rewards at higher rates than their non-drug using counterparts (Bickel et al., 1998; Bickel and Marsh, 2001; Kirby, Petry, & Bickel, 1999; Petry 2001; MacKillop, Amlung, Few, Ray, Sweet, & Munafò, 2011). Though there is evidence that substance use impacts the propensity to discount delayed rewards (Mendez, Simon, Hart, Mitchell, Nation, Wellman, & Setlow, 2010), the preponderance of evidence suggests that the propensity to discount delayed rewards precedes the development of substance use (Perry, Larson, German, Madden, & Carroll, 2005; Marusich & Bardo, 2009). Despite the lack of clarity regarding directionality (Perry & Carroll, 2008; MacKillop et al., 2011), the tendency to discount delayed rewards in favor of immediate ones is well-established in substance users and may be important in explaining the association between substance use and adherence.

Current Study

The current study examined composite substance use (heroin, cocaine, alcohol, and marijuana) as a predictor of adherence in a population of HIV positive low-income substance users in a residential treatment facility in Washington DC. We hypothesize that greater substance use severity would be significantly related to poor medication adherence. Additionally, this study aimed to examine mediators of this relationship. We hypothesize positive reinforcement from the environment and propensity for immediate rewards would mediate the inverse relationship between substance use and medication adherence.

The current study aims to address a major limitation in the extant literature- lack of investigation into mechanisms that underlie the relationship between substance use and medication adherence. The study also was designed to address other limitation such as a narrow focus on individual substances without attention to broader use across substances (e.g., Sharpe et al, 2004; Haug et al, 2005; Samet et al, 2006), thereby limiting our understanding of the effect of substance use more broadly on medication adherence. The current study will also address the limitation that studies to date have examined individuals in outpatient HIV clinics, in hospitals, or in outpatient drug treatment by examining this relationship in a population of inpatient substance users, who are at particularly high risk for low or nonadherence. As an exploratory aim, we will examine the incremental explanatory contribution of one substance as compared to another for each substance used (heroin, cocaine, alcohol, and marijuana).

Primary Aims and Hypotheses

Aim 1: To test substance use severity as a predictor of daily medication adherence in a sample of low-income substance users in residential treatment.

- a. *Hypothesis:* Higher levels of substance use will predict lower levels of medication adherence.

Aim 2: To test independent mediators of this relationship

- b. A. To test environmental rewards as a mediator of the relationship between substance use and low medication adherence.
 - 1) *Hypothesis:* Low levels of environmental reward will mediate the relationship between higher levels of substance use and lower medication adherence.
- c. To test delay discounting as a mediator of the relationship between substance use and low medication adherence.
 - 1) *Hypothesis:* Greater discounting of future rewards will mediate the relationship between higher levels of substance use and lower medication adherence.

Exploratory Aims

Exploratory Aim 1: To test both mediators (environmental rewards and delay discounting) together in a single model.

Exploratory Aim 2: To test the relationship of each substance (cocaine, opioids, marijuana, and alcohol) with daily medication adherence while controlling for the other substances.

Methods

Participants

Participants in the study were African American ($N=84$, 43.7% female) inner-city drug users ($M_{age}=45.5$, $SD=8.28$) in treatment at a residential drug treatment center, the Salvation Army Harbor Light (SAHL) Residential Treatment Center in Northeast Washington, DC. Although the percentage of female participants in this study is higher than that of females living with HIV/AIDS in the general population (CDC, 2011) this gender breakdown is consistent with that of the population of individuals living with HIV at SAHL (Chen et al., 2011). This center utilizes a mix of strategies adopted from Alcoholics and Narcotics Anonymous as well as group

sessions focused on relapse prevention. SAHL uses regular drug testing and use is grounds for dismissal from the center. HIV positive substance users who are beginning their final month of residential treatment was referred by treatment staff at the center for a randomized controlled trial investigating Behavioral Activation as a treatment for HIV medication adherence, and the current study utilizes baseline data from this trial.

Measures

Psychopathology

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 to determine study eligibility. 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.

Demographics

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

Medication Adherence

AACTG Adherence to anti-retroviral medications questionnaire (AACTG: Chesney, Morin, & Sherr, 2000). Participants read a set of directions that highlight how difficult it is for many patients to adhere to their medication regimens. Patients then provided information for each of their medications. For example, a patient would report the following information: (1) name of drug, (2) prescribed doses per day, (3) prescribed number of pills per dose, and (4) any special directions (i.e. 'with food', 'on an empty stomach' or 'with plenty of fluids'). They were next asked about the pills that they took for each of the last two days, including the name of each

medication and how many pills they had skipped that day. Patients were also asked two additional questions on more distal adherence. Patients who reported ever skipping their medications are given a list of reasons why people may miss taking their medications (e.g. had too many pills to take, wanted to avoid side effects, had a change in daily routine) and are asked to rate on a four-point scale (never, rarely, sometimes, often) how often each reason applies to them. HIV related health status will also be measured by the AACTG. Self-reported nonadherence was defined as the frequency of reasons endorsed for nonadherence across all reasons provided, with higher scores indicating greater nonadherence. This measure was used as the main self-report dependent variable of nonadherence. This is in line with other studies that have used a total reasons score as a main adherence outcome (e.g., O’Cleirigh, Ironson, & Smits, 2007; DiIorio et al., 2009; Magidson et al., 2015) in order to minimize potential inaccuracies of self-reported adherence.

Viral Load: Viral Load, an indicator of HIV disease progression, was also collected at baseline. Medication adherence was corroborated with Viral Load. Viral load has repeatedly demonstrated a significant correlation with HIV medication adherence (Arnsten et al., 2001; Glass et al., 2006; Paterson, et al., 2000), with only the most optimal rates of HIV medication adherence leading to an undetectable amount of virus in the blood stream (i.e., <50 copies/mL). These two adherence measures (self-report and viral load) were included as the dependent variables across all Aims; we treated each measure as a separate dependent variable, conducting separate analyses for all Aims.

Substance Use

Drug Use History Questionnaire (e.g., Babor & Del Boca, 1992; Grant, Contoreggi, & London, 2000; Daughters, Lejuez, Bornoalova, et al., 2005). At baseline assessment

participants were asked if they have ever used a particular substance in their lifetime, how often they used it in the past year prior to treatment, and how often they used the substance during the period of their life when they were using it most frequently. The latter two questions are rated on a 6-point scale ranging from "never", "one time", "monthly or less", "2 to 4 times a month", "2 to 3 times a week", and "4 or more times a week." All substances were assessed, but we included the most commonly used substances in this sample as the main independent variable because they are both the most prevalent substances among the sample at Harbor Light and they are also the most commonly studied substances in the literature examining substance use as it relates to HAART adherence. These included: (a) cannabis, (b) alcohol, (c) cocaine, and (d) opioids. Responses on the DUQ were summed to create an overall score of substance use severity, the main independent variable in the analyses (Tull, Bardeen, DiLillo, Messman-Moore, & Gratz, 2014).

Environmental Reward

Reward Probability Index (RPI; Carvalho et al., 2011) is a 20-item scale that is made up of two factors- Reward Probability and Environmental Suppressors. The RPI measures access to environmental rewards and response contingent positive reinforcement. Sample items include: "I have many interests that bring me pleasure", "Changes have happened in my life that have made it hard to find enjoyment", and "I have many opportunities to socialize with people". Participants are asked to rate their responses on a Likert scale ranging from "Strongly Agree" to "Strongly Disagree". The appropriate items were reverse coded, and the total score was used as our mediating variable. The RPI has high convergent validity ($r=.65-.81$) with measures of activity, avoidance, reinforcement, and depression in a sample of undergraduate students. It has also been used to measure access to environmental rewards in undergraduates with depression

(Carvalho et al., 2011), Latinos with elevated depressive symptoms (Collado, Castillo, Maero, Lejuez, & MacPherson, 2014). and HIV positive substance users in treatment (Magidson et al., 2015). Scores on the RPI comprised our mediating variable.

Delay Discounting

Monetary Choice Questionnaire (MCQ; Kirby, Petry & Bickel, 1999). Participants were presented a fixed set of 27 choices between smaller, immediate rewards and larger, delayed rewards. For example, a participant was asked, “Would you prefer \$54 today, or \$55 in 11 days?” The participant indicated which alternative he or she would prefer to receive by circling the alternative on the questionnaire. Responses on the measure were coded into small (\$25-\$35), medium (\$50-\$60), and large rewards (\$75-\$85), consistent with grouping of the reward sizes of the original measure (Kirby & Maraković, 1996). These reward magnitudes made up our mediating variable.

Data Analysis

Primary Aim 1: To test the hypothesis that substance use will have an inverse relationship with medication adherence, we employed linear regression analyses. We examined substance use severity as a predictor of medication adherence, controlling for relevant covariates. Potential covariates were identified from the set of theoretically-relevant covariates selected a priori (demographic variables, psychopathology, and HIV related health status). Variables that were significantly related to HIV medication adherence were included as covariate(s).

Primary Aims 2.a. and 2.b: To test the hypothesis that substance use will have a negative association with medication adherence and that this relation will be mediated by both environmental reward (RPI) and delay discounting (MCQ), we examined a mediation model, using the Process macro provided by Preacher and Hayes (2008) to calculate total, direct, and

indirect effects. The indirect effect of substance use on medication adherence through both RPI and MCQ in separate models will be tested using a nonparametric bootstrapping procedure (Preacher & Hayes, 2004, 2008). Bootstrapping procedures are considered preferable to other approaches because they do not assume normality of the distribution of the indirect effects and hence provide stronger protection against Type II error, compared to normal procedures such as the Sobel test (Shrout & Bolger, 2002). We determined the statistical significance of the indirect effect by examining the bootstrapped confidence intervals around this effect; confidence intervals that do not contain zero are considered significant. Potential covariates were identified from the set of theoretically-relevant covariates and were selected *a priori* (demographic variables, psychopathology, and HIV related health status). Variables that were significantly related to HIV medication adherence were included as covariate(s).

Exploratory Aim 1: If significant indirect effects (i.e. the confidence intervals do not contain zero) of substance use on medication adherence through either RPI or MCQ are established, we will then examine the relative relations between these variables using a parallel multiple mediator model following the same approach described above.

Exploratory Aim 2: We will use a hierarchical multiple regression to examine the exploratory aim of testing the relationship of each substance (cocaine, opioids, marijuana, and alcohol) with medication adherence. We entered each substance into separate regression models, with each one controlling for the other substances (and relevant covariates), to examine the incremental effect of each substance on adherence. Then we entered all substances that were significantly related to the outcome into one multiple regression model simultaneously, to examine the incremental significance of each drug on the outcome variable, medication adherence.

Results

Participants

Data were collected from 84 HIV positive (43.7% female) inner-city drug users ($M_{age}=45.5$, $SD=8.28$). Participants had been diagnosed with HIV an average of 10.24 years prior to the study ($SD=6.98$) and had an average viral load of 15700.80 ($SD=45979.28$; the virus is considered undetectable if the viral load is below 50 copies/mL). 64% of the participants were taking HIV medication daily (see Table 1 for descriptions of key study variables for those on HAART vs. not on HAART).

The number of reasons for missing doses ranged from 0-36, and participants reported an average of 11.62 reasons for missing their medication ($SD=8.8$). Additionally, 15.9% reported the last time they missed their medication was in the past week, 11% reported the last time missing their medication was 1-2 weeks prior, 6.1% reported that the last time they missed their medication was 2-4 weeks ago, 23.2% reported 1-3 months ago, 26.8% more than 3 months ago, and 17.1% reported never missing their medication. The sample was characterized by the following substance use frequencies at 4 or more times a week in the last year: Alcohol (40%), cocaine (37.3%), marijuana (14.1%), opioid (16.4%). Please see Table 1 for descriptive statistics of key study variables and bi-variate correlations, Table 2 for a detailed description of substance use frequencies during the past 12 months, and Table 3 for bi-variate correlations among substances.

Hypothesis Tests

Primary Hypothesis 1: Our first primary hypothesis was that substance use will have an inverse relationship to medication adherence. There were no significant relations among demographic or HIV related variables with adherence, and thus we did not include any

covariates in this model. The regression equation was significant, with higher substance use scores predicting lower medication adherence ($\beta=.498$, $SE=.225$, $F(1,73) =4.91$, $R^2=.063$, $p=.03$).

Primary Hypothesis 2.a: Our second primary hypothesis was that environmental reward would mediate the relation between substance use and poor medication adherence. For this test, we used a bootstrapping method for the construction of a 95% confidence interval (CI) around the unstandardized indirect effect (Hayes, 2009; Preacher & Hayes, 2008). The a path was not significant ($\beta=.159$, $F(1,73) =.51$, $R^2=.0069$, $p=.48$). The b path was significant ($\beta=-.378$, $F(2,72) =8.74$, $R^2=.20$, $p=.0004$). The c' path, or the direct effect of environmental reward on the relationship between substance use and adherence was significant ($\beta=.5583$, $SE=.2105$, $p=.0098$, CI [.139-.978]), as was the total effect ($\beta=.498$, $SE=.2248$, $p=.029$, CI [.05-.946]), however the indirect effect was not significant ($.159 \times -.378 = -.06$, CI [-.269-.082]). The indirect effect was not significant.

Primary Hypothesis 2.b. Our last primary hypothesis was that delay discounting would mediate the relation between substance use and poor medication adherence. We conducted separate analyses for small, medium, and large reward magnitude on the MCQ. The sample size for these analyses was $N=70$ due to missing data. For these tests, we also used a bootstrapping method for the construction of a 95% confidence interval (CI) around the unstandardized indirect effect (Hayes, 2009; Preacher & Hayes, 2008). The indirect effect was not significant for the small reward magnitude ($-.002 \times -4.055 = .008$, CI [-.05-.16]), medium reward magnitude ($0.00 \times -16.507 = 0$, CI [-.04-.12]), or large reward magnitude ($-.002 \times 6.993 = -.014$, CI [-.15-.02]). Thus, the hypothesis that delay discounting mediates the relation between substance use and poor medication adherence was not supported, regardless of the magnitude of the delayed reward on

the MCQ. See Figure 1 for final model of the relation between substance use and medication adherence using these mediators.

Exploratory Hypothesis 1: Because the confidence interval contained zero for both of the proposed mediators and therefore did not support an indirect effect of either environmental reward or delay discounting, we did not test them together in one model.

Exploratory Hypothesis 2: As an exploratory aim, we sought to examine the relation between each substance (alcohol, marijuana, cocaine, and opioids) and medication adherence. We used linear regression to test each drug separately. We did not control for demographic variables (e.g. age, sex) because they were not significantly related to the outcome. Past year alcohol use was significantly related to medication adherence ($\beta=1.5$, $SE=.51$, $F(1,65) = 8.89$, $R^2=.12$, $p=.004$). Past year marijuana ($\beta=.20$, $SE=.64$, $F(1,62) = .09$, $R^2=.002$, $p=.75$), cocaine ($\beta=.62$, $SE=.50$, $F(1,65) = 1.53$, $R^2=.02$, $p=.221$), and heroin use ($\beta=.27$, $SE=.59$, $F(1,63) = .21$, $R^2=.001$, $p=.818$) were not predictive of low adherence.

Biological outcomes (Viral Load):

Primary Aim 1: The regression equation examining past year substance use as a predictor of poor adherence was not significant ($\beta=668.45$, $SE=668.90$, $F(1,61) = .99$, $R^2=.016$, $p=.32$).

Primary Hypothesis 2.a: We hypothesized that environmental reward would mediate the relation between substance use and poor medication adherence as measured by high viral load. The indirect effect was the product $.077 \times 569.812 = -.06$, and the bootstrapped CI [-163.18-826.89]. Because the CI contains zero, the indirect effect was not significant and therefore this hypothesis was not supported.

Primary Hypothesis 2.b: We hypothesized that delay discounting would mediate the relation between substance use and poor HIV medication adherence. We conducted separate

analyses for small, medium, and large reward magnitude on the MCQ. For these tests, we also used a bootstrapping method for the construction of a 95% confidence interval (CI) around the unstandardized indirect effect (Hayes, 2009; Preacher & Hayes, 2008). The indirect effect was not significant for the small reward magnitude ($-.0006 \times -69099.63 = .008$; CI [-221.52-705.24]), the medium reward ($-.0001 \times -105280.39 = 0$; CI [-368.97-631.31]), or the large reward ($-.0009 \times -114032.5 = .104$; CI [-184.63-1019.98]). Because the CI contained zero for all the reward magnitudes, the indirect effects were not significant. Thus, the hypothesis that delay discounting mediates the relation between substance use and poor medication adherence was not supported, regardless of the magnitude of the delayed reward on the MCQ.

Exploratory Hypothesis 1: Because the indirect effects for the primary aims were not significant (i.e. the confidence intervals contained zero), we did not test both proposed mediators together in one model using viral load as an outcome.

Exploratory Hypothesis 2: As an exploratory aim, we sought to examine the relation between each substance (alcohol, marijuana, cocaine, and heroin) and medication adherence using viral load as an outcome. We used linear regression to test each drug separately. We did not control for demographic variables (e.g. age, sex) because they were not significantly related to the outcome. Past year alcohol use ($\beta = -3285.79$, $SE = 3224.08$, $F(1,59) = 1.04$, $R^2 = .017$, $p = .312$), marijuana use ($\beta = 156.46$, $SE = 3676.28$, $F(1,56) = .002$, $R^2 = .00$, $p = .97$), cocaine use ($\beta = 2503.60$, $SE = 3061.97$, $F(1,59) = .67$, $R^2 = .011$, $p = .417$) and heroin use ($\beta = -4419.21$, $SE = 3281.27$, $F(1,58) = 1.81$, $R^2 = .03$, $p = .18$) were not related to viral load. Because none of the substances were significantly predictive of viral load, we did not look at the relative contribution of each substance in one regression equation.

Discussion

Discussion

The purpose of this study was to examine mechanisms explaining the relation between substance use and poor medication adherence as measured by frequency of reasons for missing doses among HIV positive substance users in residential treatment. This was the first study to our knowledge that investigated mechanisms for the relation between substance use and medication adherence from a behavioral framework in a sample of HIV positive substance users. We sought to establish a temporal relationship between the independent variable (substance use), the mediating variables (environmental reward and delay discounting), and the outcome variable (medication adherence). Despite this being a theoretically and data driven hypothesis, our findings did not support mediation for either of the proposed mediators. However, we did find significant main effects of both substance use and lack of environmental reward on daily medication adherence.

Results of our study supported significant main effects of both substance use and lack of positive reinforcement from the environment on adherence, suggesting that both of these processes play a role in the maintenance of medication adherence among HIV positive substance users. Moreover, both of these constructs accounted for a substantial amount of variance in the model, suggesting that they have an additive effect on adherence as measured by frequency of reasons for missing medications. The finding that substance use is related to poor adherence is in line with our hypotheses and consistent with previous research (Arnsten et al., 2002; Malta et al., 2008; Stein et al., 2002; Gonzalez et al., 2011). Results of our study also suggest an association between lack of environmental contingencies and medication adherence as measured by frequency of reasons for missing doses. Our study is one of the first to link lack of environmental rewards to medication adherence as measured by frequency of reasons for missing doses. This

supports a behavioral theoretical framework that suggest that individuals who value a healthy, non-substance using lifestyle are more inclined to take their medication as prescribed.

The findings from our study did not support mediation with either of our proposed variables (lack of environmental reward and delay discounting). One explanation for the absence of mediation could be that there are likely reciprocal processes involved in these relationships. People who a) lack environmental contingencies and b) discount the value of a delayed reward are at risk for initiating and maintaining substance use habits, but also the regular use of substances creates an environment that lacks non-substance related reinforcement and also promotes discounting of delayed reward due to the immediate reward of using the substance. Thus, it is likely that one process increases the likelihood of another, and this pattern continues.

It is interesting that our findings did not support an association between substance use and lack of access to rewards in the environment. This finding is inconsistent with previous research. It is possible that the time of assessment affected this lack of significant findings. Participants have been in a restricted environment and thus abstinent from substances for some time. They may not exhibit the same lack of enthusiasm for non-substance related activities because they now value non-substance related activities as a result of being in drug treatment. This is consistent with findings that establish a link between abstinence and an increase in non-substance related activities (Van Etten et al. 1998).

Our findings did not support indirect effects of delay discounting on the relation between substance use and medication adherence. Results also did not support direct associations between delay discounting and substance use or delay discounting and poor adherence. The first result is surprising given the substantial body of literature that supports the relation between substance use and delay discounting (Madden et al., 1997; Mitchell, 1999; Vuchinich & Simpson, 1998;

Kirby & Petry, 2004; Yi et al., 2008), and the lack of association between delay discounting and adherence is also surprising given the strong theoretical framework that supports this relationship. There are, however factors that could explain this lack of association between delay discounting and medication adherence.

First, the delay discounting measure we used asked about immediate and delayed positive rewards, whereas medication adherence is delaying the absence of a negative reward (e.g. a delayed negative reinforcement model). Because the measure did not capture this construct, measurement limitations could explain why we did not find the association as predicted. Future studies could use a measure that is focused on delaying negative rewards. Additionally, the effect of abstinence could be a factor. Substance users who have been abstinent may not discount delayed rewards at the same rate they would have if they had been actively using during this study. In a similar vein, it could be that the substance use habits of these participants are so severe that they no longer use the substances for positive reinforcement reasons, but more so for reasons that are consistent with a negative reinforcement model of substance use. If this is the case, the value of the monetary reward would be irrelevant regardless of the delay.

Second, because we did not subdivide the reasons for nonadherence, it might be the case that delay discounting does not relate to the total composite, but rather might relate to specific domains of behavioral reasons for nonadherence (e.g. avoiding unpleasant side effects, having to keep track of a complex regimen). Previous research suggests the reasons for missing medication are in fact relevant (Magidson et al., 2015). Future research should parse apart specific reasons (e.g. intentional versus unintentional) for low adherence to examine if delay discounting could differentially predict specific reasons for nonadherence.

Regarding the exploratory aim of testing the individual contribution of each substance, we found that alcohol was the only substance that was related to low adherence. This is consistent with prior research that links alcohol use to low medication adherence among HIV positive substance users (Hendershot et al., 2009). However, we did not find that any other drug independently predicted low adherence, which raises the question of whether alcohol is driving the effect, or is it that substance use severity is the important factor, regardless of the specific substance. It is interesting that alcohol and cocaine were used at approximately the same frequency in the past year, but alcohol was significantly associated with adherence whereas cocaine was not. It could be the case that substance use severity might matter more than alcohol use on its own because it accounts for individuals using multiple substances at one time, which is common in this sample and is associated with a host of negative outcomes (Tull et al., 2014).

The findings from the study suggest two potential points for intervention, substance use and lack of access to positive rewards in the environment. Because the results did not provide specific insight regarding directionality, it would be most beneficial to provide an intervention that targets both of these risk factors. Behavioral Activation (Lejuez et al., 2011) is a promising treatment that increases access to environmental contingencies. This intervention has been proposed for individuals in residential substance use treatment to target substance use (Daughters et al., 2008), and to improve medication adherence among HIV positive substance users in residential treatment (Daughters et al., 2010). This treatment is intended to target lack of access to a rewarding environment with the goal of decreasing substance use and increasing medication adherence and is a promising treatment for this population.

Limitations and Future Directions

There are several limitations to the current study. First, because the data are cross-sectional it is difficult to investigate a true mediational model. Although there is support for cross-sectional mediation, future research should use prospective designs to examine the longitudinal effects of substance use on medication adherence. Additionally, although nonparametric bootstrapping is well suited for small samples (Preacher & Hayes, 2004, 2008a) larger sample size may be needed to detect indirect effects. Another concern is regarding the measurement of adherence. Adherence, or poor adherence, in this case was measured by assessing the frequency of reasons for missing medication. Although this measurement has been used in previous research (Magidson et al., 2015; O’Cleirigh et al., 2011), there are significant limitations to this proxy for adherence in addition to the self-report nature of the assessment. It is possible, for instance, that an individual may consistently cite one reason for nonadherence that happens regularly, while another may have a variety of reasons that happen less frequently. Additionally, reasons for missing medications may not translate to actual doses missed. Future research should examine substance use, access to environmental reward, and the propensity to discount delayed rewards in relation to a more direct measure of adherence. Another limitation regarding this outcome variable is that the reasons for missing a medication dose are not parsed apart. Risk factors for missing medication due to a behavioral reason (e.g. avoiding unpleasant side effects) could be very different from a non-behavioral reason (e.g. thinking it may not help). It is possible, for example, that delay discounting could have been related to a certain subset of reasons for missing medication, but not the composite reasons score. Future research should parse apart these reasons and investigate the differential risk factors for different types of reasons for missing doses.

Another limitation of the current study is the measure of substance use. We used past year substance use to predict overall medication adherence. It is possible that the substance use measure was too global, in averaging across more fine-grained patterns of use, to capture a lifetime of substance use and its effects on medication adherence. It is also possible that past year substance use did not mirror current substance use, and in fact the current pattern of substance use was much less frequent than in the past year prior to treatment. Future research should examine current substance use and its relation to medication adherence.

An additional limitation of the current study is that although all of the participants were HIV positive, they were not all on HAART. Although there are benefits to examining medication adherence in general (e.g. the fact that most individuals with HIV are taking additional non-HIV medications), there may be something particularly aversive about HIV medication that promotes nonadherence, thus there could be different rates of adherence for different medications, so future research should examine the effects of substance use on adherence and potential mediators using a sample of individuals all taking HAART. The current sample size was not conducive to examining only those on HAART.

A final limitation of the current study may have been the setting. Data were collected in a residential substance use treatment center, which is a restricted environment. This could have an effect on medication adherence because it is a controlled environment with access to a nursing staff who could help manage adherence. This environment also may also be misrepresentative of past year substance use because the participants are often entering the treatment facility from another restricted environment, where drug use is prohibited. Together, these factors may limit generalizability to the general substance using population with HIV. Nonetheless, this study provides insight into the risk factors for poor medication adherence among HIV positive

substance users in residential treatment and provides opportunities for further research and targeted clinical interventions.

Future research should address the limitations of the current study including measures of substance use and nonadherence, and timing of the assessments. There is also a need for prospective studies that examine substance use and medication adherence overtime in order to examine possible mediators at various time points and to examine the ways by which medication adherence is affected by a lifetime of substance use. Future research might also look at additional mediators and moderators of the relation between substance use and low adherence, including psychopathology. For instance, there is a strong literature to suggest a relation between depression and anxiety and low medication adherence among individuals with HIV/AIDS (Safren et al., 2012). There is also a strong relationship between depression and lack of access to environmental contingencies, so depression might be a factor that could be incorporated into the model in the current study.

To conclude, the current study sought to extend previous research on the relation between substance use and poor medication adherence among HIV positive substance users by examining possible mechanism that could explain this relationship, environmental rewards and delay discounting. Though neither of our mediation models was supported, this study did shed light on the processes that contribute to low adherence, namely substance use and lack of environmental contingencies. Consistent with a behavioral framework, access to environmental contingencies is imperative when considering the complexity of reasons for missing daily medication. Future research is needed to address the limitations of and to extend the current study in order to gain a complete picture of the processes that contribute to low adherence among vulnerable populations, namely HIV positive substance users in residential treatment.

Bibliography

- Altice, F. L., Kamarulzaman, A., Soriano, V. V., Schechter, M., & Friedland, G. H. (2010). Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. *The Lancet*, *376*(9738), 367-387.
- Ammassari, A., Trotta, M. P., Murri, R., Castelli, F., Narciso, P., Noto, P., ... & Antinori, A. (2002). Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *Journal of acquired immune deficiency syndromes*, *31*, 123-127.
- Arnsten, J. H., Demas, P. A., Farzadegan, H., Grant, R. W., Gourevitch, M. N., Chang, C. J., et al. (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: Comparison of self-report and electronic monitoring. *Clinical Infectious Diseases*, *33*, 1417-1423.
- Arnsten, J. H., Demas, P. A., Grant, R. W., Gourevitch, M. N., Farzadegan, H., Howard, A. A., & Schoenbaum, E. E. (2002). Impact of Active Drug Use on Antiretroviral Therapy Adherence and Viral Suppression in HIV-infected Drug Users. *Journal of general internal medicine*, *17*(5), 377-381.
- Bandura, A., & Walters, R. H. (1963). Social learning and personality development.
- Bandura, A. (1969). Principles of behavior modification.
- Bangsberg, D. R. (2006). Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clinical Infectious Diseases*, *43*, 939-941.
- Bangsberg, D. R., Perry, S., Charlebois, E. D., Clark, R. A., Roberston, M., Zolopa, A. R. et al. (2001). Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*, *15*, 1181-1183.

- Babor, T., & Del Boca, F. (1992). Just the facts: enhancing measurement of alcohol consumption using self-report methods. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods*, 3-19.
- Bornovalova, M. A., Daughters, S. B., Hernandez, G. D., Richards, J. B., & Lejuez, C. W. (2005). Differences in impulsivity and risk-taking propensity between primary users of crack cocaine and primary users of heroin in a residential substance-use program. *Experimental and Clinical Psychopharmacology*, 13(4), 311-318.
- Bickel, W. K., Madden, G. J., & Petry, N. M. (1998). The price of change: The behavioral economics of drug dependence. *Behavior Therapy*, 29(4), 545-565.
- Bickel, W.K., Marsch, L.A. (2001). Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction*, 96, 73–86.
- Bing, E., Burnam, A., Longshore, D., Fleishman, J., Sherbourne, C., London, A., et al. (2001). Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of General Psychiatry*, 58, 721–728.
- Carroll, M. E., & Comer, S. D. (1996). Animal models of relapse. *Experimental and Clinical Psychopharmacology*, 4(1), 11-18.
- Carvalho, J. P., Gawrysiak, M. J., Hellmuth, J. C., McNulty, J. K., Magidson, J. F., Lejuez, C. W., & Hopko, D. R. (2011). The reward probability index: design and validation of a scale measuring access to environmental reward. *Behavior therapy*, 42(2), 249-262.
- Centers for Disease Control and Prevention. (2012). Fast Facts. Retrieved from:
http://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/
- Centers for Disease Control and Prevention (CDC; 2011). “HIV surveillance report: Diagnoses of HIV infection and AIDS in the United States and Dependent Areas,” *Volume 21*.

- Chesney, M. A., Ickovics, J. R., Chambers, D. B., Gifford, A. L., Neidig, J., Zwickl, B., Wu, W., & the Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). (2000a). Self-reported adherence to antiretroviral medications among participants in the HIV clinical trials: the AACTG Adherence Instruments. *AIDS Care, 12*, 255-266.
- Chesney, M.A. (2000). Factors affecting adherence to antiretroviral therapy. *Clinical Infectious Diseases, 30*, 171–176.
- Chesney, M. (2003). Adherence to HAART regimens. *AIDS patient care and STDs, 17*(4), 169-177.
- Collado, A., Castillo, S. D., Maero, F., Lejuez, C. W., & MacPherson, L. (2014). Pilot of the brief behavioral activation treatment for depression in Latinos with limited English proficiency: preliminary evaluation of efficacy and acceptability. *Behavior therapy, 45*(1), 102-115.
- Correia, C. J., Benson, T. A., & Carey, K. B. (2005). Decreased substance use following increases in alternative behaviors: A preliminary investigation. *Addictive Behaviors, 30*(1), 19-27.
- Crum, N. F., Riffenburgh, R. H., Wegner, S., Agan, B. K., Tasker, S. A., Spooner, K. M., et al. (2006). Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *Journal of Acquired Immune Deficiency Syndromes, 41*, 194-200.
- Daughters, S. B., Lejuez, C. W., Bornoalova, M. A., Kahler, C., Strong, D., & Brown, R. (2005). Distress tolerance as a predictor of early treatment dropout in a residential substance abuse treatment facility. *Journal of Abnormal Psychology, 114*, 729-734.

- Daughters, S. B., Magidson, J. F., Schuster, R. M., & Safren, S. A. (2010). ACT HEALTHY: A combined cognitive-behavioral depression and medication adherence treatment for HIV-infected substance users. *Cognitive and Behavioral Practice, 17*, 309-321.
- DiIorio, C., McCarty, F., Depadilla, L., Resnicow, K., Holstad, M. M., Yeager, K. et al. (2009). Adherence to antiretroviral medication regimens: a test of a psychosocial model. *AIDS and Behavior, 13*, 10-22.
- District of Columbia Department of Health (DOH). (2010). *Annual Report 2010*. Retrieved from http://www.dchealth.dc.gov/doh/frames.asp?doc=/doh/lib/doh/services/administration_of_fices/hiv_aids/pdf/2010_Annual_Report_FINAL.pdf
- First, M. B., & Gibbon, M. (2004). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). In: Hilsenroth, M. J. & Segal, D. L. (Eds.), *Comprehensive handbook of psychological assessment, Vol. 2: Personality assessment*. Hoboken, NJ: John Wiley & Son.
- Fogarty, L., Roter, D., Larson, S., Burke, J., Gillespie, J., & Levy, R. (2002). Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Education and Counseling, 46*, 93-108.
- Garcia de Olalla, P., Knobel, H., Carmona, A., Guelar, A., Lopez-Colomes, J. L., & Cayla, J. A. (2002). Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes, 30*, 105-110.
- Glass, T. R., De Geest, S., Weber, R., Vernazza, P. I., Rickenbach, M., Furrer, H., et al. (2006). Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected

- patients: the Swiss HIV Cohort Study. *Journal of Acquired Immune Deficiency Syndrome*, 41, 385-92.
- Golin, C. E., Liu, H., Hays, R. D., Miller, L. G., Beck, C. K., Ickovics, J., Kaplan, A. H., & Wenger, N. S. (2002). A prospective study of predictors of adherence to combination antiretroviral medication. *Journal of General Internal Medicine*, 17, 756-765.
- Gonzalez, J. S., Psaros, C., Batchelder, A., Applebaum, A., Newville, H., & Safren, S. (2011). Clinician-assessed depression and HAART adherence in HIV-infected individuals in methadone maintenance treatment. *Annals of Behavioral Medicine*, 42, 120-126.
- Grant, S., Contoreggi, C., & London, E. (2000). Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia*, 38(8), 1180-1187.
- Haug N. A., Sorensen J. L., Lollo N. D., Gruber V. A., Delucchi K. L., Hall S. M. (2005). Gender differences among HIV-positive methadone maintenance patients enrolled in a medication adherence trial. *AIDS Care*, 17, 1022–1029.
- Heil, S. H., Johnson, M. W., Higgins, S. T., & Bickel, W. K. (2006). Delay discounting in currently using and currently abstinent cocaine-dependent outpatients and non-drug-using matched controls. *Addictive Behaviors*, 31(7), 1290-1294.
- Higgins, S. T., Heil, S. H., & Lussier, J. P. (2004). Clinical implications of reinforcement as a determinant of substance use disorders. *Annual Review of Psychology*, 55, 431-461.
- Hinkin, C. H., Hardy, D. J., Mason, K. I., Castellon, S. A., Durvasula, R. S., Lam, M. N., & Stefaniak, M. (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS*, 18, 19-25.
- Hinkin, C. H., Barclay, T. R., Castellon, S. A., Levine, A. J., Durvasula, R. S., Marion, S. D., ...

- & Longshore, D. (2007). Drug use and medication adherence among HIV-1 infected individuals. *AIDS and Behavior*, *11*(2), 185-194.
- Hosmer Jr, D. W., & Lemeshow, S. (2004). *Applied logistic regression*. John Wiley & Sons.
- Kirby, Kris N., and Nino N. Maraković. "Delay-discounting probabilistic rewards: Rates decrease as amounts increase." *Psychonomic bulletin & review* 3.1 (1996): 100-104.
- Kirby, K. N., Petry, N. M., & Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *Journal of Experimental Psychology: General*, *128*(1), 78-87.
- Kirby, K. N., & Petry, N. M. (2004). Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addiction*, *99*(4), 461-471.
- Knowlton, A. R., Arnsten, J. H., Eldred, L. J., Wilkinson, J. D., Shade, S. B., Bohnert, A. S., ... & Purcell, D. W. (2010). Antiretroviral Use among active injection-drug users: The role of patient-provider engagement and structural factors. *AIDS patient care and STDs*, *24*(7), 421-428.
- Kuo, I., Greenberg, A. E., Magnus, M., Phillips, G., Rawls, A., Peterson, J., et al. (2011). High prevalence of substance use among heterosexuals living in communities with high rates of AIDS and poverty in Washington, DC. *Drug and Alcohol Dependence*, *117*, 139-144.
- MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., & Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta analysis. *Psychopharmacology*, *216*(3), 305-321.
- Madden, G. J., Petry, N. M., Badger, G. J., & Bickel, W. K. (1997). Impulsive and self-control choices in opioid-dependent patients and non-drug-using control participants: Drug and monetary rewards. *Experimental and Clinical Psychopharmacology*, *5*, 256-262.

- Magidson, J. F., Linstead, A., Seitz-Brown, C. J., Safren, S. A., Lejuez, C. W., & Daughters, S. B. (2015). Can behavioral theory inform the understanding of depression and medication nonadherence among HIV-positive substance users?. *Journal of behavioral medicine, 38*(2), 337-347.
- Malta, M., Strathdee, S. A., Magnanini, M. M., & Bastos, F. I. (2008). Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review. *Addiction, 103*(8), 1242-1257.
- Marusich, J. A., & Bardo, M. T. (2009). Differences in impulsivity on a delay discounting task predict self-administration of a low unit dose of methylphenidate in rats. *Behavioural pharmacology, 20*(5-6), 447.
- Maxwell, S. E., & Cole, D. A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods, 12*, 23-44.
- McGowan, C. C., Weinstein, D. D., Samenow, C. P., Stinnette, S. E., Barkanic, G., Rebeiro, P. F., ... & Hulgan, T. (2011). Drug use and receipt of highly active antiretroviral therapy among HIV-infected persons in two US clinic cohorts. *PloS one, 6*(4), 1-8.
- Meade CS, Conn NA, Skalski LM, Safren SA. (2011). Neurocognitive impairment and medication adherence in HIV patients with and without cocaine dependence. *Journal of Behavioral Medicine, 31*, 128–138.
- Mendez, I. A., Simon, N. W., Hart, N., Mitchell, M. R., Nation, J. R., Wellman, P. J., & Setlow, B. (2010). Self-administered cocaine causes long-lasting increases in impulsive choice in a delay discounting task. *Behavioral neuroscience, 124*(4), 470.
- Miller, L. G., & Hays, R. D. (2000). Measuring adherence to antiretroviral medications in clinical trials. *HIV Clinical Trials, 1*, 36-46.

- Mitchell, S. H. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology, 146*, 455–464.
- Murphy, J. G., Correia, C. J., Colby, S. M., & Vuchinich, R. E. (2005). Using behavioral theories of choice to predict drinking outcomes following a brief intervention. *Experimental and clinical psychopharmacology, 13*(2), 93.
- O’Cleirigh, C., Ironson, G., & Smits, J. A. (2007). Does distress tolerance moderate the impact of major life events on psychosocial variables and behaviors important in the management of HIV? *Behavior Therapist, 38*, 314-323.
- Palepu, A., Horton, N. J., Tibbetts, N., Meli, S., & Samet, J. H. (2004). Uptake and adherence to highly active antiretroviral therapy among HIV-infected people with alcohol and other substance use problems: the impact of substance abuse treatment. *Addiction, 99*(3), 361-368.
- Paterson, D., Swindells, S., Mohr, J., Brester, M., Vergis, E., Squier, C., et al. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine, 133*, 21-30.
- Peretti-Watel, P., Spire, B., Lert, F., & Obadia, Y. (2006). Drug use patterns and adherence to treatment among HIV-positive patients: evidence from a large sample of French outpatients. *Drug and alcohol dependence, 82*, 71-79.
- Perry, J. L., Larson, E. B., German, J. P., Madden, G. J., & Carroll, M. E. (2005). Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. *Psychopharmacology, 178*(2-3), 193-201.
- Perry, J. L., & Carroll, M. E. (2008). The role of impulsive behavior in drug abuse. *Psychopharmacology, 200*(1), 1-26.

- Petry, N. M. (2001). Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. *Psychopharmacology*, *154*, 243-250.
- Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers*, *36*(4), 717-731.
- Preacher, K. J., & Hayes, A. F. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior research methods*, *40*(3), 879-891.
- Reynolds, N. R. (2004). Adherence to antiretroviral therapies: State of the science. *Current HIV Research*, *2*, 207-214.
- Safren, S. A., O'Cleirigh, C., Tan, J. Y., Raminani, S. R., Reilly, L. C., Otto, M. W., & Mayer, K. H. (2009). A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. *Health Psychology*, *28*(1), 1-10.
- Samet, J. H., Horton, N. J., Meli, S., Freedberg, K. A., & Palepu, A. (2006). Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. *Alcoholism, Clinical and Experimental Research*, *28* (4), 572-577.
- Sharpe T. T., Lee L. M., Nakashima A. K., Elam-Evans L. D., Fleming P. L. (2004). Crack cocaine use and adherence to antiretroviral treatment among HIV-infected black women. *Journal of Community Health*, *29*, 117-127.
- Shrout, P. E., & Bolger, N. (2002). Mediation in experimental and nonexperimental studies: new procedures and recommendations. *Psychological methods*, *7*(4), 422-445.
- Shuter, J., Sarlo, J. A., Kanmaz, T. J., Rode, R. A., & Zingman, B. S. (2007). HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of

- virologic suppression despite adherence rates less than 95%. *Journal of Acquired Immune Deficiency Syndromes*, 45, 4-8.
- Skeer, M. R., Mimiaga, M. J., Mayer, K. H., O'Cleirigh, C., Covahey, C., & Safren, S. A. (2012). Patterns of substance use among a large urban cohort of HIV-infected men who have sex with men in primary care. *AIDS and behavior*, 16(3), 676-689.
- Skinner, B. F. (1953). *Science and human behavior*. Simon and Schuster.
- Stein, M., Rich, J., Maksad, J., Chen, M., Hu, P., Sobota, M., & Clarke, J. (2000). Adherence to antiretroviral therapy among HIV-infected methadone patients: effects of ongoing illicit drug use. *American Journal of Drug and Alcohol Abuse*, 26, 195–205.
- Tull, M. T., Bardeen, J. R., DiLillo, D., Messman-Moore, T., & Gratz, K. L. (2014). A Prospective Investigation of Emotion Dysregulation as a Moderator of the Relation between Posttraumatic Stress Symptoms and Substance Use Severity. *Journal of Anxiety Disorders*, In Press.
- Van Etten ML, Higgins ST, Budney AJ, Badger GJ. 1998. Comparison of the frequency and enjoyability of pleasant events in cocaine abusers vs. non-abusers using a standardized behavioral inventory. *Addiction* 93(11):1669–80.
- Vuchinich, R. E., & Simpson, C. A. (1998). Hyperbolic temporal discounting in social drinkers and problem drinkers. *Experimental and clinical psychopharmacology*, 6, 292-305.
- Yi, R., Johnson, M. W., Giordano, L. A., Landes, R. D., Badger, G. J., & Bickel, W. K. (2008). The effects of reduced cigarette smoking on discounting future rewards: An initial evaluation. *The Psychological Record*, 58, 163-174.