

# **Predictors of One-Year Cognitive Decline in a Marginally Housed, Multimorbid Sample**

by

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# Approval

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## Ethics Statement



The author, whose name appears on the title page of this work, has obtained, for the research described in this work, either:

- a. human research ethics approval from the Simon Fraser University Office of Research Ethics

or

- b. advance approval of the animal care protocol from the University Animal Care Committee of Simon Fraser University

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## **Abstract**

Marginal housing is associated with high prevalence of several morbidities, including viral infection, psychiatric diagnosis and substance use, each of which is known to compromise cognition. The nature or course of cognition in marginally housed persons is understudied, and the impact of comorbidity on cognition is often unaddressed in the literature. Over a period of one year, participants recruited from the Downtown Eastside of Vancouver evidenced generally stable cognitive performance, except for a slight improvement in sustained attention and a slight decline in cognitive flexibility. HIV seropositive individuals showed declines in memory and response inhibition, while cannabis dependence was marginally associated with decline in memory. Given the negative impact of cognitive impairment on functioning, these results can inform prioritization of treatment targets in multimorbid populations.

**Keywords:** marginal housing; comorbidity; HIV; cannabis dependence; cognition; longitudinal

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# Table of Contents

Approval.....	ii
Ethics Statement.....	iii
Abstract.....	iv
Acknowledgements.....	v
Table of Contents.....	vi
List of Tables.....	vii
List of Figures.....	viii
<b>Chapter 1. Introduction .....</b>	<b>1</b>
<b>Chapter 2. Method .....</b>	<b>6</b>
2.1. Participants.....	6
2.2. Procedure.....	6
2.2.4 Cognitive Measures .....	6
Memory.....	6
Response inhibition.....	7
Attention.....	7
Decision-making.....	7
Cognitive flexibility.....	8
2.2.1 Infection Measures.....	8
2.2.3 Substance Dependence.....	9
2.2.2 Substance Use Measures.....	9
2.3. Analytic Approach.....	10
<b>Chapter 3. Results .....</b>	<b>12</b>
3.1. Sample Characteristics.....	12
3.2. Acute substance use and cognitive change.....	15
3.3. Characterization of cognitive change.....	15
3.4. Factors associated with cognitive decline.....	17
Memory.....	17
Response inhibition.....	20
Attention.....	22
<b>Chapter 4. Discussion .....</b>	<b>23</b>
<b>References .....</b>	<b>29</b>
Appendix A: Psychiatric diagnosis criteria.....	37
Appendix B: Acute substance use effects.....	38

## List of Tables

Table 1.	Sample Characteristics .....	13
Table 2.	Cognitive Performance at Baseline and Follow-up .....	16
Table 3.	Correlations between Candidate Independent Variables and Cognitive Change Scores.....	18

## List of Figures

Figure 1.	Mean Change Scores for Memory by HIV Status and Cannabis Dependence.....	19
Figure 2.	Mean Change Scores for Response Inhibition by HIV Status .....	21



# Chapter 1.

## Introduction

In recent years, there has been an increase in urban centres in the prevalence of marginal housing, defined as low-income accommodations characterized by limited privacy and a lack of secure tenancy (Grigg, Judd, Ryan & Komiti, 2005; Shannon, Ishida, Lai & Tyndall, 2006). Single room occupancy (SRO) hotels are a form of marginal housing which are particularly common in urban areas, and are characterized by low barriers to tenancy, substandard conditions and insecure tenancy, with many residents oscillating between homelessness and SRO residency (Shannon et al., 2006). These hotels are often a last resort for those with limited income and resources, and SRO residents represent some of society's most disadvantaged populations. In marginally housed populations, there is increased prevalence of several health risks, including higher rates of substance use, viral infections and psychiatric illness (Fazel, Khosla, Doll & Geddes, 2008; Shannon et al., 2006; Vila-Rodriguez et al., 2013). The co-occurrence of multiple morbidities is common in this population; previous work by our group in a sample of SRO residents found that the median number of illnesses, including viral infection, psychiatric diagnosis, and neurological condition, was three, and less than 20 percent of individuals presented with only one morbidity (Vila-Rodriguez et al., 2013). Furthermore, an increase in number of morbidities was associated with poorer real-world functioning (Vila-Rodriguez et al., 2013). However, research on the impact of multimorbidity on cognition is limited; thus there is currently an incomplete understanding of the degree to which individuals with multiple morbidities are at increased risk for cognitive problems. Marginally housed populations may be at particular risk for such increased problems given their notably high rates of multimorbidity. Cognition in marginally housed populations is generally understudied (as has been noted by others in our group; Gicas et al., 2014) and to date there are no studies on the longitudinal course of cognition in this population. The aims of the present study are to examine the impact

of several critical health-related variables on the trajectory of cognitive decline over one year in a marginally housed sample.

Several of the health risks that are particularly prominent in the present marginally housed sample, namely viral infection, substance use and psychiatric illness, have well-established relationships with cognitive dysfunction. HIV infection is associated with impairments in a variety of cognitive domains, with the largest deficits seen in processing speed, attention, memory and executive functions (Grant, 2008; Woods, Moore, Weber & Grant, 2009). Hepatitis C (HCV) infection is related to poorer functioning in several facets of cognition, including attention, working memory and processing speed, and there is growing evidence that these impairments are associated with multiple dynamic mechanisms of the virus and are present even in individuals without liver damage (Perry, Hilsabeck & Hassanein, 2008). Impairments in numerous cognitive domains are observed with chronic substance use (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011). Major mental illness is also associated with decreased cognitive functioning for various diagnoses, including schizophrenia (Palmer, Dawes & Heaton, 2009) which is present in increased rates in marginally housed populations (Vila-Rodriguez et al., 2013). However, these morbidities have differential effects on cognitive course over time, whereby the impairments seen in major psychiatric disorders tend to remain stable (Palmer et al., 2009; Quraishi & Frangou, 2002), while untreated HIV infection (Reger et al., 2002) and HCV infection (Perry et al., 2008) and chronic substance use (Fernández-Serrano et al., 2011) are associated with progressive cognitive decline.

Limited prior cross-sectional and longitudinal research suggests that comorbidity increases the risk of cognitive impairment and decline associated with the aforementioned illnesses. In HIV seropositive groups, cross-sectional studies have demonstrated that comorbidities appear to negatively modify cognitive abilities, covering several primary domains. Although extensive research on the impact of comorbid HIV infection and substance use on cognition has not been conducted, as others have noted (Basso & Bornstein, 2000; Martin-Thormeyer & Paul, 2009), there is evidence for additive effects. In persons who are seropositive for HIV infection, comorbid alcohol use disorder is associated with cognitive impairment in multiple cognitive domains (Martin-

Thormeyer & Paul, 2009). Similarly, methamphetamine use is associated with exacerbation of general cognitive impairment in HIV seropositive individuals (Carey et al., 2006; Rippeth et al., 2004). Some research has suggested additive effects of cannabis use on cognitive impairment, primarily in memory (Cristiani, Pukay-Martin & Bornstein, 2004), and one study found poorer performance on a sustained attention task in HIV seropositive cocaine users (Levine et al., 2006). Polysubstance users who are HIV seropositive are more impaired on tasks of working memory (Farinpour et al., 2000; Martin et al., 2001), decision-making (Martin et al., 2004), prospective memory (Martin et al., 2007) and complex motor skills (Gonzalez et al., 2008) than those who are seronegative. In terms of other comorbidities, individuals who are co-infected with both HIV and HCV tend to have poorer cognitive performance in several domains and have higher rates of cognitive impairment than those who are monoinfected with either (Martin-Thormeyer & Paul, 2009; Giesbrecht et al., 2014; Perry et al., 2008). Considering the other morbidities prevalent in our sample, others have noted that there is limited research on the effects of comorbid HCV infection and substance use (Devlin et al., 2012), and on comorbidities in substance users (Fernández-Serrano et al., 2011).

Thus although there are significant gaps in the literature, the limited existent research indicates that comorbidity in populations with viral infections and substance use may be associated with additional cognitive impairment. Furthermore, there is evidence from longitudinal studies that comorbidity is associated not only with greater cognitive impairment but also with exacerbation of the cognitive decline that is associated with viral infections and substance use. To date this research is primarily limited to HIV-positive populations. In one of the few previous longitudinal studies of an HIV-infected sample with other comorbidities, health factors associated with increased risk of cognitive decline in HIV seropositive persons included a diagnosis of methamphetamine use, depressive symptoms, and absence of antiretroviral treatment (Heaton et al., 2015). Depressive symptoms in individuals with HIV have also been associated with failure to show cognitive improvement over two years (Gibbie et al., 2006). Another study found that one-year cognitive decline in Chinese HIV seropositive participants was associated with variables related to infection including HIV viral plasma load but not to HCV infection, although HCV was associated with greater cognitive impairment at baseline (Cysique et al., 2010). Therefore certain comorbidities, including substance use, are

associated with increased risk for cognitive decline in HIV seropositive persons, but critical gaps concerning the longitudinal impact of comorbidity in other disorders remains unaddressed.

The present investigation is the first study to our knowledge examining cognition longitudinally in a marginally housed sample. This work will extend the existing research into the cognitive effects of several comorbidities that include but are not limited to HIV. Marginally housed populations present with increased rates of numerous morbidities, including viral infection and substance use, and there is ample evidence for the detrimental effects on cognition of each of these morbidities individually. Research on the effects of comorbidity is more limited but provides evidence for exacerbation of the cognitive decline associated with singular morbidities. The aims of the present study were to investigate the nature of cognition longitudinally in a marginally housed sample and examine specific morbidities as risk factors for cognitive decline within the context of marginal housing and comorbidity.

Given the paucity of literature on cognition in marginally housed samples, the first aim of the present study was to characterize the nature of cognitive change in a marginally housed sample of persons with multiple morbidities. This aim will focus on evaluating whether cognition remains stable or declines over the period of one year. The second aim is to evaluate the risk conveyed by specific morbidities on cognitive decline. Of the numerous morbidities present in the sample, those that have been associated with progressive cognitive deterioration in prior research were examined to determine their association with cognitive decline in a marginally housed, multimorbid sample. Specifically, these morbidities included HIV (Reger et al., 2002) and HCV infection (Perry et al., 2008) and chronic substance use (Fernández-Serrano et al., 2011). It was anticipated that presence of these particular morbidities would be associated with cognitive decline, while individuals without these morbidities were expected to show relatively stable cognitive performance over one year. Finally, based on prior research documenting the aggregate negative impacts of comorbidity on HIV-associated cognitive decline (Cysique et al., 2010; Gibbie et al., 2006; Heaton et al., 2015), the presence of additional cognitive decline in individuals with multiple morbidities was anticipated. Drawing on the limited literature documenting the detrimental impacts

of comorbidities on cognitive decline in HIV seropositive samples, it was anticipated that comorbidity for viral infection and substance use would be associated with greater cognitive decline in comparison to individuals with only one of those risk factors.

The present study will expand the existing literature on the longitudinal impacts of comorbidity in marginally housed populations to determine the degree to which comorbidity exacerbates the cognitive decline associated with viral infection and substance use. An increased understanding of the impact of various morbidities on cognition will be valuable for informing treatment priorities and appraising potential impacts on real-world functioning in this understudied population.

## Chapter 2.

### Method

#### 2.1. Participants

Three-hundred and eighty-four individuals were recruited as part of an ongoing, ten-year longitudinal study (see Vila-Rodriguez et al., 2013, for a detailed description of the study and sample). The current study used data from the time period between the baseline and first follow-up cognitive assessments (approximately one year). Participants were recruited from single room occupancy hotels in a marginalized neighbourhood in downtown Vancouver, British Columbia, with the only inclusion criteria being ability to communicate in English. Informed consent was obtained and participants were given a small honorarium. These hotels constitute substandard housing and many of the individuals living in them have a history of past homelessness. The study has been previously approved by the ethics board of the University of British Columbia and Simon Fraser University.

#### 2.2. Procedure

**2.2.4 Cognitive Measures.** A neuropsychological battery was administered at baseline and at follow-up which occurred approximately one year after baseline (months  $M = 13.13$ ,  $SD = 2.96$ ). Cognitive measures included verbal memory, response inhibition, attention, decision-making and cognitive flexibility. At the time of cognitive assessment, information on age, gender and education was also collected.

**Memory.** Verbal memory was measured by total recall scores on the Hopkins Verbal Learning Test Revised (HVLTR; Brandt & Benedict, 2001), using alternative

forms at baseline and follow-up. This portion of the HVLTR consists of three immediate recall trials; in each trial participants are read a list of 12 words, from three different semantic categories, and then immediately asked to recall as many as they can. For this analysis, the total recall score, the sum of words recalled on each of the three trials, was used. The HVLTR has demonstrated adequate reliability (test-retest reliability correlations in the range of .55-.78 for the total recall score; Benedict, Schretlen, Groninger, & Brandt, 1998) and validity, correlating with other measures of verbal memory ( $r = .75$  with the Logical Memory subtest of the Wechsler Memory Scale-Revised; Shapiro, Benedict, Schretlen, & Brandt, 1999).

**Response inhibition.** Scores on the Color-Word Trial of the Stroop task (Golden & Freshwater, 2002) were used to measure response inhibition. Participants are presented with printed names of colours in an ink colour different to that of the word. They must name the colour of ink each word is printed in, and the total number of words named in a 45-second time period is the outcome measure.

**Attention.** Attention was assessed with the Rapid Visual Information Processing (RVIP) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB), in which participants view a series of digits on a screen and respond to a target sequence (Fray, Robbins, & Sahakian, 1996; Sahakian & Owen, 1992). The RVIP has demonstrated strong test-retest correlations ( $r = .76-.80$ ; Lowe & Rabbit, 1998) and moderate correlations with other tests of executive function ( $r = .35$ ; Smith, Need, Cirulli, Chiba-Falek, & Attix, 2013). The A prime score was used as the performance measure for this task; this score is a measure of participant's successful detection of target sequences, based on the probability of hits and false alarms.

**Decision-making.** The Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994) was used to assess reward-based decision-making. On a computer participants played with four decks of cards. Turning each card is associated with mock monetary reward and sometimes also with a penalty. Immediate feedback as well as a running total of net gains and losses is displayed on the screen. Two of the decks are associated with higher reward but also higher loss through penalties, making them disadvantageous in the long run. The other two decks are associated with lower

rewards and lower loss, making them ultimately more advantageous. The task is terminated once 100 cards have been selected. A net score was calculated by subtracting the total number of cards played in the two disadvantageous decks from the total played in the advantageous decks. Evidence for validity of the IGT is indicated by performance differences in individuals with decision-making impairments, such as those with damage to areas of the frontal lobe related to decision-making (Buelow & Suhr, 2009). The IGT has been associated with real-life functioning as assessed by addiction severity (Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006).

**Cognitive flexibility.** The Intra-Extra Dimensional Set Shift (IED) test from the CANTAB (Sahakian & Owen, 1992) was used to assess executive functions. In this task, two stimuli appear on the computer screen and the participant selects one by touching it. Participants receive immediate feedback as to whether their response was correct or incorrect which helps them determine the rule for selection. After six consecutive correct selections, the rule changes without the participant's awareness. An extra dimension is later added to the stimuli and the rule switches between the dimensions. The task ends after the ninth stage or when six consecutive correct responses have not been made within 50 trials of any stage. Acceptable test-retest reliability ( $r = .70$ ; Lowe & Rabbitt, 1998) and moderate correlations with other measures of executive functioning ( $r = -.26$ ; Smith et al., 2013) have been demonstrated. For this task two performance measures were used: the number of errors summed across all stages that were completed at both baseline and follow-up, and the number of stages completed.

**2.2.1 Infection Measures.** At baseline, serology was used to assess presence of antibodies for HIV and hepatitis C. For those participants who were Hepatitis C seropositive, quantitative polymerase chain reaction (qpcr) was assessed to determine whether the infection was active. Presence of liver fibrosis and cirrhosis was also ascertained by calculating the AST to platelet ratio index (APRI). Consistent with similar calculations previously reported by our group (Vila-Rodriguez et al., 2013), the APRI was calculated using the local laboratory upper limit of normal (which equaled 35), and APRI raw scores were categorized according to the following criteria: an APRI greater than 0.7 was considered indicative of fibrosis, and an APRI greater than 2



indicative of cirrhosis. Serology assessing liver damage was completed at both baseline and follow-up.

**2.2.3 Substance Dependence.** Diagnoses of psychiatric illness, including substance dependence, depression, schizophrenia and schizoaffective disorder, were made at baseline by a psychiatrist, using the Best Estimate Clinical Evaluation and Diagnosis (BECED; Endicott, 1988), which takes into account information obtained from all sources, including hospital records and the other assessments that were administered. The latter included the Mini-International Neuropsychiatric Interview (Lecrubier et al., 1997), the International Personality Disorder Examination, Screener (Lenzenweger, Loranger, Korfine, & Neff, 1994), the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1988), the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), and the Trauma History Questionnaire (Mueser et al., 2001). Diagnoses using the BECED were made in accordance with the *Diagnostic and Statistical Manual* (4<sup>th</sup> ed; *DSM-IV-TR*; American Psychiatric Association, 2000; see Appendix A for a description of diagnostic criteria for relevant disorders).

**2.2.2 Substance Use Measures.** Chronic substance use was assessed monthly using the Time-Line Follow-Back (TLFB) method, in which participants report frequency (number of days per week) of illicit substance and prescription medication use during the past 4 weeks. This measure of substance use has been tested in a homeless sample, revealing strong test-retest reliability ( $r = .77-.89$ ), and validity as assessed by correlation to another self-report drug use interview (kappa coefficients ranging from .66-.79) and consistency with clinician diagnoses and ratings of severity of use (Sacks, Drake, Williams, Banks, & Herrell, 2003). Previous work by our group has also demonstrated high consistency between the TLFB and urine drug screens in the current sample (Jones et al., 2013). Time-Line Follow-Back data was used to ascertain use of methamphetamine, cocaine, heroin, cannabis, alcohol, and adherence to prescribed antiretroviral medications. Numbers of days of use per month was averaged over the time period between baseline and follow-up cognitive assessment. Four groups were created for each substance: participants who reported zero days of use for a given substance were put into one group, and the remaining participants were split into equal groups based on 33<sup>rd</sup> and 66<sup>th</sup> percentile splits. The rationale for this transformation of

the days of use variable was based upon the non-normal distribution of the raw variable as well as systematic visual inspection of the data suggesting that other approaches were inadequate (e.g., a dichotomous split between users and non-users).

Acute substance use for the 48 hours prior to neuropsychological testing was assessed on the day of testing by urinalysis and self-report. Urine drug screening was conducted on the day of assessment and was used to detect cannabis, cocaine, amphetamines, methamphetamine, MDMA, opiates, barbiturates, benzodiazepines, and tricyclic antidepressants. Self-report information was collected via a structured interview which inquired about type of substances consumed in the past 48 hours.

### **2.3. Analytic Approach.**

To characterize cognitive change for the overall sample, separate pairwise t-tests were conducted for each cognitive variable. Subsequently, cognitive change scores were created for use in the following analyses. For all of the cognitive measures except the IED, difference scores were created by subtracting baseline performance from follow-up performance. For the IED, a composite score was created combining two measures of performance available for this task: number of errors per stage, and number of stages completed. Error difference scores were created by subtracting the number of errors at follow-up from the number of errors at baseline for each stage, for only those stages that were completed at both time-points. Difference scores for the number of stages completed were created by subtracting the number of stages completed at baseline from the number of stages completed at follow-up. The correlation between these indices was very high ( $r = .96, p < .05$ ). Both sets of difference scores were standardized to Z scores, the sets of Z scores summed, and the sum was also standardized to a Z score. This was done in order to increase the sensitivity of the score to change in performance by combining two available measures of performance on the task, and to minimize skew and kurtosis, which were present in the individual difference scores.

A series of analyses were conducted to identify variables that are associated with increased risk for cognitive decline. Candidate independent variables that have been

associated with cognitive decline in prior literature were selected to undergo pre-screen. These included HIV and HCV infection, substance dependence diagnoses, and use of alcohol, cannabis, cocaine, methamphetamine and heroin.

These variables were first screened for association with the cognitive change scores by examining partial correlations (controlling for age, gender and education) between candidate independent variables and cognitive change scores. A minimum of 1.5% overlap in variance (or  $r = .12$ ) was set as the criterion for inclusion in further analyses. This criterion was chosen based on expectations that minimal changes in cognition would generally be present over the relatively short time period of one year, given that cognitive performance is typically fairly stable. Consequently, the limited variance in cognitive change may be weakly associated with predictor variables; nonetheless, this variance is important to predict. Prior to conducting the main analyses, baseline differences were evaluated for candidate variables that met pre-screen criteria. For the main analyses, variables meeting the pre-screen criteria were investigated in an initial ANCOVA, in which age, gender and education were entered as covariates. Covariates that did not emerge as significant in the initial model were not included in the final model. Prior to running the main analyses, all cognitive change scores were screened for the effects of acute substance use at the time of assessment.

## Chapter 3. Results

### 3.1. Sample Characteristics.

Of the 384 participants enrolled in the study, 350 completed baseline cognitive assessment and 288 completed follow-up cognitive assessment within 24 months of baseline assessment. Follow-up duration ranged from 6 to 24 months, with a mean of 13.71 months. Follow-up duration was not related to cognitive change scores for any of the cognitive domains (all  $r < .12$ ,  $p > .05$ ). Of those who completed follow-up assessment, 92.36 % ( $n = 266$ ) had HVLT-R data that was valid at both time-points, 88.54 % ( $n = 255$ ) had Stroop data that was valid at both time-points, 76.74 % ( $n = 221$ ) had valid RVP data, 81.60 % ( $n = 235$ ) had valid IED data, and 65.28 % ( $n = 188$ ) had valid IGT data. Demographic characteristics and percentages for the health variables are displayed in Table 1; slight fluctuations in the  $n$  are due to varying amounts of missing data for different variables.

**Table 1. Sample Characteristics**

	Mean (SD)	% of n
Age (years) <sup>a</sup>	44.70 (9.27)	
Gender (% male) <sup>a</sup>		77.40
Education (years) <sup>a</sup>	10.36 (2.28)	
<b>Viral infection</b>		
HIV <sup>b</sup>		18.10
Antiretroviral treatment at baseline		66.70
Hepatitis C (ever had) <sup>b</sup>		69.00
Hepatitis C (currently active) <sup>c</sup>		43.80
Liver fibrosis <sup>b</sup>		16.40
Liver cirrhosis <sup>b</sup>		4.60
<b>Psychiatric diagnosis</b>		
Schizophrenia or schizoaffective disorder <sup>a</sup>		14.80
Depressive disorder <sup>a</sup>		30.60
Bipolar disorder <sup>a</sup>		8.70
Alcohol dependence <sup>a</sup>		17.70
Cannabis dependence <sup>a</sup>		30.90
Stimulant dependence <sup>a</sup>		84.40
Opiate dependence <sup>a</sup>		42.70
Traumatic brain injury <sup>d</sup>		22.80
<b>Substance use (days of use/month)</b>		
<b>Alcohol<sup>e</sup></b>		
Alcohol dependent	5.69 (8.03)	
Non-alcohol dependent	0.98 (2.34)	
<b>Cannabis<sup>f</sup></b>		
Cannabis dependent	12.49 (10.29)	
Non-cannabis dependent	3.37 (6.25)	
<b>Cocaine<sup>f</sup></b>		
Stimulant dependent	10.35 (9.73)	
Non-stimulant dependent	1.58 (4.10)	
<b>Methamphetamine<sup>f</sup></b>		
Stimulant dependent	3.08 (5.78)	
Non-stimulant dependent	0.50 (2.04)	
<b>Heroin<sup>f</sup></b>		
Opiate dependent	6.52 (8.87)	

Non-opiate dependent	4.67 (0.11)
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*Note:* <sup>a</sup>  $n = 288$ . <sup>b</sup>  $n = 281$ . <sup>c</sup>  $n = 201$ . <sup>d</sup>  $n = 250$ . <sup>e</sup>  $n = 286$ . <sup>f</sup>  $n = 285$ .

### **3.2. Acute substance use and cognitive change.**

Pre-screening for acute substance use revealed that there were minimal effects of acute substance use on cognitive change scores, with the exception of the RVIP and HVLT-R (see Appendix B for a detailed description of results). Five participants were removed from the RVIP analyses who were on tricyclic antidepressants and showed change scores that were lower than the other participants,  $F(3, 195) = 4.85, p < .01$ , partial  $\eta^2 = 0.07$ . For the HVLT-R, there was a main effect of acute cannabis use,  $F(3, 237) = 3.41, p < .05$ , partial  $\eta^2 = 0.04$ , driven by higher change scores in the group who used cannabis at baseline but not at follow-up. Subsequent analyses with the HVLT-R tested whether results were different when this group of participants were excluded from the sample (see below).

### **3.3. Characterization of cognitive change.**

In order to characterize the nature of cognitive change for the overall sample, separate pairwise t-tests were conducted to compare baseline and follow-up scores for the HVLT-R, Stroop, RVP and IGT. Wilcoxon signed rank tests, a non-parametric counterpart of dependent t-tests, were used for the IED variables because these data were not normally distributed. Raw score means at baseline and follow-up are displayed in Table 2. There was no difference in performance at baseline versus follow-up for the Stroop,  $t(254) = 1.19, p > .05$ , IGT,  $t(187) = 0.85, p > .05$ , or HVLT-R,  $t(246) = 1.80, p > .05$ . In contrast, there was a significant improvement in RVIP performance from baseline to follow-up,  $t(214) = 3.46, p < .05$ . For the IED, the total errors score was higher at follow-up than at baseline,  $z = -2.71, p < .05$ , while there was no difference between the number of stages completed,  $z = -0.73, p > .05$ .

**Table 2. Cognitive Performance at Baseline and Follow-up**

Cognitive domain	Baseline			Follow-up	
	<i>n</i>	<i>M (SD)</i>	Range	<i>M (SD)</i>	Range
Memory (HVLTR)	266	18.97 (5.54)	4 - 31	19.54 (5.91)	0 - 36
Response inhibition (Stroop)	255	35.55 (9.84)	9 - 63	36.16 (10.98)	8 - 68
Attention (RVP)*	221	.86 (.06)	.63 - .99	.88 (.06)	.63 – 1.00
Decision-making (IGT)	188	-5.19 (32.25)	-100 – 100	-2.61 (37.04)	-94 – 100
Cognitive flexibility (IED)	228				
Total errors**		26.08 (15.36)	0-74	29.33 (13.61)	2-93
Stages completed		7.40 (1.88)	1-9	7.29 (1.97)	0-9

*Note.* All means reported are raw scores (HVLTR total recall raw score; Stroop colour-word raw score; RVP A'; IGT net score; IED stages completed; total errors, the sum of errors across only those stages which were completed at both baseline and follow-up). \*  $p < .05$  for dependent t-test comparing means at baseline and follow-up; \*\* $p < .05$  for Wilcoxon signed-rank test for comparison of non-parametric data.



### 3.4. Factors associated with cognitive decline.

Pre-screening results are displayed in Table 3. For the cognitive domains of decision-making and cognitive flexibility, there were no candidate variables that met pre-screen criteria, and therefore these variables were not analyzed further.

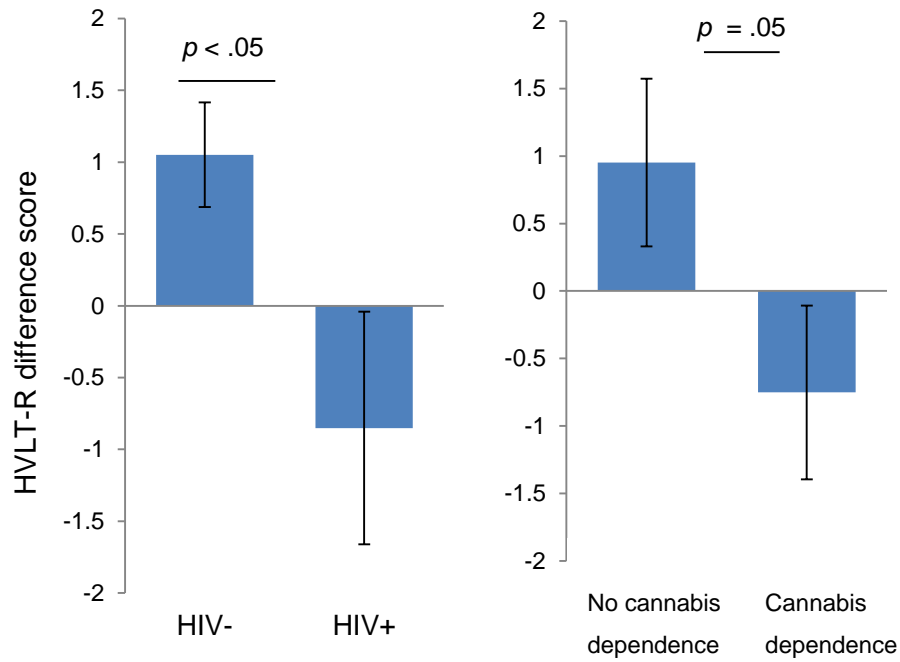
**Memory.** For the HVLT-R, candidate independent variable that met pre-screen criteria included HIV ( $r = -.14, p < .05$ ) and cannabis dependence ( $r = -.16, p > .05$ ). Baseline memory performance was comparable between HIV seropositive ( $M = 18.05, SD = 5.32, n = 43$ ) and seronegative ( $M = 19.00, SD = 5.51, n = 218$ ) groups,  $t(259) = 1.04, p > .05$ , and between those with cannabis dependence ( $M = 18.97, SD = 5.38, n = 111$ ) and those without ( $M = 18.75, SD = 5.57, n = 150$ ),  $t(259) = 0.33, p > .05$ . The initial 2 (HIV Status) x 2 (cannabis dependence) ANCOVA with age, gender and education as covariates, indicated that none of the covariates contributed to change in memory (all  $p > .35$ ) and they were dropped from the analysis. Subsequently, a 2x2 ANOVA revealed a main effect of HIV,  $F(1, 257) = 4.58, p < .05$ , partial  $\eta^2 = 0.02$ , and a marginal effect of cannabis dependence,  $F(1, 257) = 3.77, p = .05$ , partial  $\eta^2 = 0.01$ . As displayed in Figure 1, HIV seropositive persons recalled fewer words at follow-up than at baseline ( $M = -0.84, SD = 5.78$ ), in contrast to seronegative persons, who recalled more words ( $M = 1.05, SD = 5.21$ ). As shown in Figure 1, participants with cannabis dependence recalled marginally ( $p = .05$ ) fewer words at follow-up than at baseline ( $M = -0.75, SD = 5.32$ ), while an improvement in recall was present in persons without cannabis dependence ( $M = 0.96, SD = 5.28$ ). The cannabis dependence by HIV status interaction was not significant,  $F(1, 257) = 0.07, p > .05$ . These analyses were re-run to test whether change in liver function over the follow-up duration was confounded with the cognitive effects of viral infection. This was done because liver damage has been associated with cognitive impairment in prior literature (Collie et al., 2005) and may be confounded with viral infection. Participants ( $n = 38$ ; 12 HIV-positive) were removed who either changed in liver function status (normal liver function, fibrosis, or cirrhosis) from baseline to follow-up, or who evidenced change in APRI scores at a level previously identified as a threshold for cognitive decline (i.e. a change of 0.5 or greater; Valcour et al., 2016). When participants who evidenced changing liver function were removed from the analysis, the effect of HIV remained,  $F(1, 219) = 5.39, p < .05$ , partial  $\eta^2 = 0.02$ . For

**Table 3. Correlations between Candidate Independent Variables and Cognitive Change Scores**

<b>Illness characteristic</b>	<b>Memory</b>	<b>Response inhibition</b>	<b>Attention</b>	<b>Decision-making</b>	<b>Cognitive flexibility</b>
<b>Viral infection</b>					
HIV infection	-.14*	-.13*	-.02	.09	.02
HCV infection	.01	.002	.13	-.09	.02
<b>Substance dependence</b>					
Alcohol dependence	.02	-.09	.05	-.02	-.07
Cannabis dependence	-.16*	-.03	.06	-.06	.08
Opiate dependence	.05	-.10	-.01	-.01	-.03
<b>Substance use (days of use/month)</b>					
Alcohol	-.02	-.06	.02	.02	-.05
Cannabis	.02	.02	.06	-.05	.07
Cocaine	-.05	-.11*	.03	.07	-.05
Heroin	-.03	-.02	-.01	.02	.01
Methamphetamine	.10	.11	-.02	-.09	.09

*Note.* All correlations are partial correlations controlling for age, gender and education. \* $p < .05$ .

**Figure 1. Mean Change Scores for Memory by HIV Status and Cannabis Dependence**

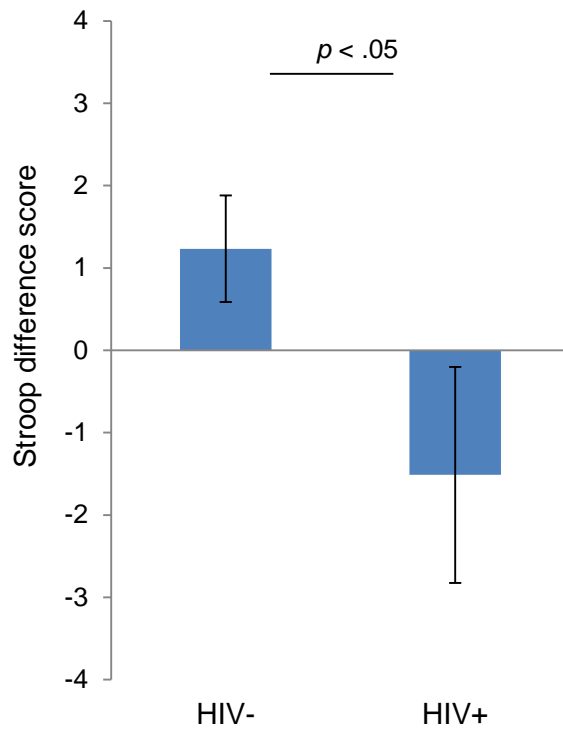


*Figure 1.* Mean change scores for HVLTR total recall raw score over approximately one year in HIV seropositive ( $n = 43$ ) and HIV seronegative groups ( $n = 218$ ), and in those with ( $n = 111$ ) and without ( $n = 150$ ) a diagnosis of cannabis dependence.  $P$  values are from main effects analyses in ANOVA. Error bars represent standard errors.

cannabis dependence, the pattern of differences in means remained the same, and the effect was still not statistically significant,  $F(1, 219) = 3.23, p = .07$ , partial  $\eta^2 = 0.01$ . When participants who used cannabis at baseline and not at follow-up ( $n = 18$ ) were removed from the analyses, the results for cannabis dependence were comparable, whereby the cannabis dependent group showed a marginal decline in memory performance ( $M = -0.17, SD = 5.18$ ) contrasted to the group that was not cannabis dependent ( $M = 1.21, SD = 4.75$ ),  $F(1, 238) = 3.80, p = .05$ , partial  $\eta^2 = 0.02$ . For HIV, the same pattern of results was observed whereby the HIV seropositive group showed a decline ( $M = -0.75, SD = 5.92$ ) and the HIV seronegative group improved ( $M = 0.89, SD = 4.74$ ), but the effects were no longer statistically significant,  $F(1, 238) = 3.02, p = .08$ , partial  $\eta^2 = 0.01$ . In order to further examine the memory decline associated with HIV infection, a subsequent analysis was performed to test the association between antiretroviral treatment and cognition in the HIV seropositive group. In the HIV seropositive group, there was no association between mean days of antiretroviral medication use per month and change in memory performance ( $r = -.05, p > .05$ ).

**Response inhibition.** HIV status was the only candidate independent variable identified in pre-screen with Stroop task change scores,  $r = -.13, p < .05$ . At baseline, there was no difference in performance between the HIV seropositive ( $M = 34.79, SD = 9.80$ ) and seronegative ( $M = 35.57, SD = 9.92$ ),  $t(248) = 0.47, p > .05$  groups. In an initial ANCOVA with age, gender, and education as covariates and HIV status (seropositive:  $n = 43$ ; seronegative:  $n = 207$ ) as the independent variable, the only covariate that contributed to change in response inhibition was gender,  $F(1, 240) = 4.71, p < .05$ , partial  $\eta^2 = 0.02$ , therefore the other covariates were not included in further analyses. A subsequent ANCOVA identified a main effect of HIV,  $F(1, 241) = 3.97, p < .05$ , partial  $\eta^2 = 0.02$ . As shown in Figure 2, HIV seropositive individuals showed a slight decline in scores from baseline to follow-up ( $M = -1.53, SD = 8.24$ ), in contrast to HIV seronegative persons, who showed a slight improvement ( $M = 1.18, SD = 7.99$ ). In the HIV seropositive group, there was no association between mean days of antiretroviral use per month and change in response inhibition ( $r = .14, p > .05$ ). As with the memory analyses, these analyses were re-run to test whether change in liver function over the follow-up duration was confounded with the cognitive effects of viral infection. Participants ( $n = 35, 12$  HIV-positive) were removed from the analysis who either

**Figure 2. Mean Change Scores for Response Inhibition by HIV Status**



*Figure 2.* Mean change scores for Stroop colour-word raw score over approximately one year in participants with ( $n = 43$ ) and without ( $n = 207$ ) HIV infection.  $P$  values are from main effects analyses in ANOVA. Error bars represent standard errors.

changed in liver function status, or who evidenced an APRI change of 0.5 or greater. The means and variances were comparable when excluding these participants (HIV negative:  $M = 1.15$ ,  $SD = 8.01$ ; HIV positive:  $M = -1.53$ ,  $SD = 8.60$ ), but the effect was no longer statistically significant,  $F(1, 212) = 2.87$ ,  $p = .09$ , partial  $\eta^2 = 0.01$ .

**Attention.** Hepatitis C antibody exposure ( $r = .13$ ,  $p < .05$ ) was the only candidate variable that met the pre-screen criteria in the RVIP analyses. At baseline, there was no difference in performance between those who were seropositive for HCV antibodies ( $M = 0.86$ ,  $SD = 0.06$ ) and those who were seronegative ( $M = 0.87$ ,  $SD = 0.06$ ),  $t(210) = 1.19$ ,  $p > .05$ . In an initial ANCOVA with age, gender and education as covariates, and Hepatitis C (presence of antibodies:  $n = 148$ ; absence of antibodies:  $n = 64$ ) as the independent variable, gender was the only significant covariate,  $F(1, 207) = 6.21$ ,  $p < .05$ , partial  $\eta^2 = 0.03$ , therefore the other covariates were not included in subsequent analyses. In a second ANCOVA, the effect for Hepatitis C was not statistically significant,  $F(1, 207) = 3.41$ ,  $p > .05$ , partial  $\eta^2 = 0.02$ . These analyses were re-run to test whether change in liver function over the follow-up duration was confounded with the cognitive effects of viral infection. Participants ( $n = 34$ , 30 Hepatitis C-positive) were removed who either changed in liver function status, or who evidenced an APRI change of 0.5 or greater. This analysis revealed a similar null effect of Hepatitis C,  $F(1, 175) = 3.61$ ,  $p > .05$ , partial  $\eta^2 = 0.02$ . A follow-up ANCOVA with gender as the covariate was conducted to test the association between current infection status (active HCV infection, cleared HCV infection, or never had HCV), and this effect was also not significant,  $F(2, 207) = 2.35$ ,  $p > .05$ , partial  $\eta^2 = 0.02$ .

## Chapter 4. Discussion

Individuals living in marginalized housing often experience multiple health issues that are known to individually compromise cognition, but there is limited research on the cognitive functioning of marginally housed populations and on the effects of multimorbidity. This is one of the first studies to examine cognition longitudinally in a marginally housed, multimorbid sample. Among the numerous morbidities present in the sample, those that have been associated with continuous cognitive compromise in prior research, including HIV (Reger et al., 2002) and HCV infection (Perry et al., 2008) and chronic substance use (Fernández-Serrano et al., 2011), were expected to show an association with one-year cognitive decline in the present study. Based on prior research documenting the additional negative impact of comorbidity (Cysique et al., 2010; Gibbie et al., 2006; Heaton et al., 2015), cognitive decline was expected to be greater in individuals comorbid for viral infections and substance use. In the overall sample, cognitive performance remained stable over the course of one year, showing neither decline nor improvement, in the domains of memory, response inhibition, and decision-making. A small improvement was observed on a task of sustained attention and a slight decline was present on one of the scores (total errors) derived from a cognitive flexibility task. Of the numerous morbidities present in this sample, HIV infection and a marginal effect of cannabis dependence were associated with declines in select cognitive domains. Further, there was no evidence of a synergistic effect that aggregates decline when both of these comorbidities were present.

HIV infection in this sample was associated with declines in memory and possibly response inhibition, although the latter effect may have been confounded with variable liver function over the follow-up duration in the sample. The detrimental effects of HIV on cognition have been well documented and include impairments in several core cognitive domains (Woods et al., 2009), including mild to moderate impairments in memory (Reger et al., 2002) and deficits in various facets of executive functioning

including response inhibition (Hinkin, Castellon, Hardy, Granholm & Siegle, 1999). HIV infection within the brain is most commonly found in the basal ganglia, hippocampus, white matter and frontal cortex (Schouten, Cinque, Gisslen, Reiss, & Portgies, 2011), and some of these abnormalities have been related to adverse cognitive functioning (Ragin et al., 2005). In the present study, the mean decline in the HIV seropositive group was slightly less than one raw score point in memory and 1.5 raw score points in response inhibition, corresponding to declines of 0.16 and 0.19 of the overall sample standard deviation, respectively. These declines are smaller than those observed in cognitively impaired populations; for example, mild cognitive impairment has been associated with a decline of approximately 0.5 of a standard deviation over the course of one year (Storandt, Grant, Miller, & Morris, 2006). However, the decline observed in HIV seropositive persons suggests the presence of early cognitive deterioration that warrants further attention over longer time frames. Further analyses of this sample in the later years of the study will serve to elucidate whether this rate of decline persists.

In recent years, the impact of HIV on cognition has been significantly ameliorated by the advent of combination antiretroviral therapy (Schouten et al., 2011). However, we did not find an association between antiretroviral adherence and differential decline, suggesting that in this sample greater antiretroviral adherence was not associated with alleviation of the detrimental impacts of HIV. Although various studies have demonstrated that the use of antiretroviral therapy may mitigate cognitive decline (e.g. Heaton et al., 2015), it does not eradicate it, as milder forms of impairment persist (Schouten et al., 2011). This may be due to potential neurotoxic effects of antiretroviral therapy, and different capacities for central nervous system penetration in different medications (Schouten et al., 2011). These results suggest that, among individuals with multiple comorbid health issues, the presence of HIV infection is one of the key morbidities that is associated with decline over the period of one year, and that mere adherence to antiretroviral medication does not mitigate this decline observed in HIV seropositive individuals.

A diagnosis of cannabis dependence was marginally associated with a decline (0.14 of a standard deviation) in memory performance. Although the extent to which cannabis impacts cognition is controversial, the cognitive domain in which there is the



most conclusive evidence for a detrimental impact is memory, where small effect sizes have been noted (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003). Heavy long-term cannabis use has been associated with reduced hippocampal and amygdala volume (Yücel et al., 2008), and animal studies have demonstrated neurotoxic effects of cannabis within the hippocampus with prolonged administration (e.g. Lawston, Borella, Robinson, & Whitaker-Azmitia, 2000). Interestingly, self-reported frequency of cannabis use for the interval between baseline and follow-up cognitive assessment did not show an association with memory decline. This may be partially because the self-report nature of this assessment introduced additional error into this measure, despite evidence from prior research that the Time-Line Follow-Back demonstrates adequate reliability and validity in a sample similar to ours (Sacks et al., 2003). An additional or alternative explanation may be that a diagnosis of cannabis dependence is associated with other parameters of cannabis use that may be more predictive of memory impairments than past-year frequency, such as higher dose (Bolla, Brown, Eldreth, Tate, & Cadet, 2002) or longer lifetime history of use.

It is somewhat surprising that no substances other than cannabis dependence emerged with even a marginal association with cognitive decline in a sample in which use of more harmful substances is prevalent. The substances and corresponding dependence diagnoses examined included heroin, cocaine, methamphetamine, cannabis and alcohol, and of these, only a cannabis dependence diagnosis emerged as having a marginal relationship with any of the cognitive domains. Many of these other substances, such as opiates and methamphetamine, have stronger associations with memory impairments than cannabis in prior literature (Baldacchino, Balfour, Passetti, Humphris, & Matthews, 2012; Scott et al., 2007). Due to the lack of longitudinal research on cognition in active substance users, there is little information on the disparate rate of decline associated with various substances, but it is possible that the null findings resulted from differential rates of decline associated with particular substances. Future research, including the continuation of the present study beyond one year, can help to differentiate the nature and course of cognition in different substances.

Changes in performance in the domains of sustained attention, decision-making and mental flexibility did not show a relationship with any of the health-related variables assessed in the present study. Partially because of the nature of tasks designed to measure executive functions, these tasks, which often involve aspects of novel problem-solving, may be less reliable than other, more traditional neuropsychological measures such as the HVLТ-R and Stroop task. Additionally, it is possible that decline in these cognitive domains occurs over a more gradual time course that is not well captured within the relatively short time span of one year.

The only domain in which the sample as a whole demonstrated improvement from baseline to follow-up was the task of sustained attention (RVIP from the CANTAB), where a small effect size was observed. In previous research, medium effect sizes have been noted for practice effects over a period of three months for learning and memory, attention and executive functions (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). Practice effects for neuropsychological testing are often studied under considerably shorter timeframes than one year, typically ranging from weeks to months. Few studies have examined practice effects over longer time periods therefore the extent to which such findings generalize to longer follow-up durations is unclear, or whether practice effects persist after this amount of time at all. Some research suggests that there is no practice effect in the HVLТ-R after one year (Woods et al., 2005), while another study found practice effects ranging from 0.2 to 0.1 standard deviations after 15 months in various cognitive domains (Machulda et al., 2013). It is possible that the lack of practice effects in most of the cognitive domains observed in this sample is simply due to the longer timeframe utilized in this study compared to most research examining practice effects. However, there is a growing body of evidence that lack of practice effects, typically studied under shorter time periods such as a few days to weeks, is associated with presence of cognitive impairment (Darby, Maruff, Collie, & McStephen, 2002) and reduced practice effects are predictive of poorer future cognitive performance (Newman et al., 2001; Duff et al., 2007; Duff et al., 2010; Duff et al., 2011). It is possible that the lack of practice effects observed in our sample is also reflective of underlying cognitive pathology or weakness, although given the limited research on typical one-year practice effects, it is unclear at this time to what degree their observed absence in this sample is abnormal. Although the reliable change index is a common method of

accounting for expected practice effects, this approach is primarily used to assess change at the individual level in clinical settings, and is not relevant to designs with control groups, which were present in our main analyses. Furthermore, the extent to which the test-retest reliabilities reported in the literature are applicable to this study is debatable given the unique nature of the present sample. Thus in the present study, in which control groups were used and test-retest reliabilities were questionably applicable, the reliable change index would not have been an appropriate method of analysis.

An important limitation of this study is that some of the factors examined may not have a substantial impact on decline over one year; their emergence as nonsignificant in this study does not preclude the possibility that they impact cognition in a more gradual course such that the rate of decline is only detectable over a longer time span. Future work, including the extension of our analyses to the later years of our study, should aim to identify the impacts of multiple morbidities on the trajectory of cognitive decline over a longer time period. The lack of effect observed for antiretroviral adherence may be partially due to the fact that medication adherence may not be a sufficiently accurate proxy for viral load because factors such as drug resistance may confound the relationship between adherence and immunosuppression (Cysique & Brew, 2009), and because the mitigating effect of antiretroviral medication varies across type of medication (Schouten et al., 2011), and this sample was prescribed a variety of different types of antiretroviral medication. A significant limitation of the current work is that other, more dynamic measures of HIV infection and current status of immunosuppression, including CD4 count and viral load, were not available. Tasks of executive function are notoriously more difficult to examine longitudinally due to their unique focus on novel problem-solving, and it is conceivable that additional noise present in these variables rendered the detection of merely small effects difficult. Despite the additional challenges associated with evaluation of change in executive functioning, it remains important to include this key domain in studies of cognition. An alternative approach to the ANCOVA analyses used in this study could include multivariate regression models, but this approach would not have afforded any additional benefit as the ANCOVA models also allowed for full analysis simultaneously of all independent variables of interest (i.e. those meeting pre-screen criteria).

A characterization of the impact of various comorbidities and their interactions on the course of cognition can inform prioritization of treatment targets. Knowledge of the cognitive status and risk factors for decline in marginally housed, multimorbid populations is highly relevant to treatment, as neuropsychological functioning is implicated in real-world functioning and treatment outcomes. In substance users, impairments on a variety of cognitive domains, including executive functions and impulsivity, are associated with shorter retention in cognitive behavioural therapy (Aharonovich, Nunes, & Hasin, 2003) and rehabilitation centers among cocaine users (Stevens et al., 2013). In HIV infection, neuropsychological impairments in several domains are associated with decreased functioning in terms of vocational abilities (van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999), medication adherence (Albert et al. 1999; Hinkin et al., 2002; Levine et al., 2005), driving (Marcotte et al., 2004) and other activities of daily living (Heaton et al., 2004). Treatments that target the appropriate cognitive deficits could be used to enhance treatment outcomes. For example, the use of memory devices and cognitive remediation strategies have been shown to improve medication adherence in persons with HIV (Andrade et al., 2005) and response to treatment in substance users (Sofuoglu, DeVito, Waters, & Carroll, 2013).

In conclusion, cognitive performance in a group of marginally housed, multimorbid individuals remained relatively stable in the sample as a whole over the course of approximately one year. Declines in memory were associated with HIV infection and marginally with cannabis dependence, while declines in response inhibition were associated with HIV infection only. Although approximately 65% of HIV seropositive individuals were treated with antiretroviral medications, adherence was not associated with mitigation of the observed cognitive decline. Future work will elucidate the degree to which these early indicators of cognitive compromise are associated with progressive decline over longer time frames in multimorbid samples.

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## **Appendix A: Psychiatric diagnosis criteria.**

Substance dependence according to *DSM-IV-TR* criteria is characterized by the presence of a minimum of three of the following occurring within the same 12-month period: tolerance; withdrawal; taking the substance in greater amounts or over a longer period than was intended; unsuccessful attempts to control use; significant amount of time spent to obtain, use or recover from the substance; important social, recreational or occupational activities are diminished due to use; continued use despite negative consequences (American Psychiatric Association [APA], 2000).

Major depressive disorder according to *DSM-IV-TR* criteria is characterized by the presence of a minimum of five of the following for a minimum 2-week period: depressed mood or loss of pleasure (at least one of these must be present); weight loss or gain, or appetite change; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate, or indecisiveness; suicidal ideation; the symptoms must cause clinically significant distress or impairment in functioning (APA, 2000).

Schizophrenia according to *DSM-IV-TR* criteria is characterized by the presence of two or more of the following for a minimum 6-month period: delusions; hallucinations; disorganized speech; grossly disorganized or catatonic behaviour; negative symptoms (e.g. avolition, affective flattening, alogia); marked reduction in self-care or functioning (APA, 2000).

Schizoaffective disorder according to *DSM-IV-TR* criteria is characterized by the following: the presence of a mood episode (major depressive, manic or mixed episode) concurrent with symptoms that meet diagnostic criteria for schizophrenia; the presence of delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms; mood episode symptoms are present for a substantial portion of the total duration of the active and residual periods of the illness (APA, 2000).

## Appendix B: Acute substance use effects.

To screen for the possible effects of acute substance use at the time of cognitive testing, a separate one-way ANCOVA was conducted for each of the cognitive variables. Urinalysis data was used to assess acute substance use, and for participants for whom urinalysis was missing (14.37% at baseline, 16.14% at follow-up), data from the questionnaire administered at assessment was used instead. This was done in order to maximize sample size, and was justified given the generally strong agreement observed between urinalysis and self-report (see Tables A1 and A2).

Four groups were created to characterize concordance between acute use at the time of baseline assessment and at follow-up assessment: a group that had not used at either baseline or follow-up (no use), a group that had used at baseline but not at follow-up (baseline use), a group that had not used at baseline but had used at follow-up (follow-up use), and those who had used at both baseline and follow-up (use at both time-points). A separate ANCOVA for each cognitive variable was run to test the effects of different levels of acute substance use, with the cognitive change scores as the dependent variable, the acute substance use variables as the independent variable, and age, gender and education as covariates.

For the Stroop, IED and IGT, there was no main effect of acute use for any of the substances. For the HVLt-R, there was a main effect of acute cannabis use,  $F(3, 237) = 3.41$ ,  $p < .05$ , partial  $\eta^2 = 0.04$ . Post-hoc comparisons using a Bonferroni correction revealed that the group of participants who used cannabis at baseline but not at follow-up had higher mean change scores ( $M = 4.98$ ,  $SD = 8.66$ ) than the group who did not use cannabis at all ( $M = 0.88$ ,  $SD = 4.80$ ). Because there was a large discrepancy between sample sizes in the different groups (no use:  $n = 150$ ; use at both time-points:  $n = 70$ ; use at baseline only:  $n = 18$ ; use at follow-up only:  $n = 25$ ), this effect was not modeled in further analyses but analyses were tested to determine whether results differed when this group of participants was excluded from the sample.

For the RVIP, there was a significant main effect of tricyclic antidepressant use,  $F(3, 195) = 4.85$ ,  $p < .01$ , partial  $\eta^2 = 0.07$ . Post-hoc comparisons using Bonferroni correction revealed that the group who used tricyclic antidepressants at both time-points ( $M = -0.07$ ,  $SD = 0.06$ ) had higher mean change scores than the no use group ( $M = 0.03$ ,  $SD = 0.05$ ) and marginally higher scores than the follow-up use group ( $M = 0.03$ ,  $SD = 0.06$ ). Because sample sizes between the four groups were highly discrepant (no use:  $n = 203$ ; use at both time-points:  $n = 5$ ; use at baseline only:  $n = 6$ ; use at follow-up only:  $n = 5$ ), this variable was not modeled in further analyses but the participants who used tricyclic antidepressants at both time-points ( $n = 5$ ) were excluded from further analyses with the RVP.

**Table A1: Agreement between self-report of acute (past 48 hour) substance use and urinalysis on the day of baseline cognitive assessment (N = 307)**

<b>Substance</b>	<b>Agreement between self-report and urinalysis (κ)</b>
Amphetamine	.09**
Cocaine	.55**
Marijuana	.67**
Methamphetamine	.66**
MDMA	.15**
Opiates	.60**

\*p < .05 \*\* p < .005

**Table A2: Agreement between self-report of acute (past 48 hour) substance use and urinalysis on the day of follow-up cognitive assessment**

<b>Substance</b>	<b>Agreement between self-report and urinalysis (κ)</b>
Amphetamine	.07*
Cocaine	.47**
Marijuana	.67**
Methamphetamine	.15**
MDMA	a
Opiates	.57**

\*p < .05 \*\* p < .005

a No statistics calculated because 0 participants self-reported MDMA use (13 were positive on urinalysis)