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The Influence of Neurocognitive Impairment on HIV Treatment Outcomes among Drug-involved People Living with HIV/AIDS

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Abstract

Findings to date indicate that it is feasible to deliver a brief behavioral risk reduction/medication adherence group intervention to HIV-infected IDUs in a community-based setting. HIV infection and substance abuse can result in neurocognitive impairment and this is directly relevant to intervention development because a significant number of people living with HIV/AIDS have a positive history of substance abuse and being able to successfully participate in behavioral interventions often requires a relatively high level of cognitive performance. The aim of the current study was to evaluate if changes in information, motivation and behavior skills with respect to medication adherence, sex- and drug-risk behavior outcomes from baseline to post-intervention is predicted by cognitive impairment following the brief 4-session Holistic Health for HIV intervention for HIV-infected Drug Users (3H+). Significant associations were found between change in motivation and certain neurocognitive performance domains. Findings suggest that it may be helpful to specifically tailor such behavioral interventions to accommodate cognitive impairment.

INTRODUCTION

Unprotected sex and sharing of unsterilized injection equipment are currently the main modes of HIV transmission. In the US, men who have sex with men (MSM), heterosexual intercourse, and injection drug use (IDU) are the major modes of HIV transmission. HIV infection and substance abuse can each independently result in neurocognitive impairment (NCI; Al-Zahrani & Elsayed, 2009; Aydin, Kircan, Sarwar, Okur, & Balaban, 2009; Foley, Ettenhofer, Wright, & Hinkin, 2008; I. Grant, Heaton, & Atkinson, 1995). In combination, they have an even more profound effect on the central nervous system (Margolin, Avants, Warburton, & Hawkins, 2002; Norman, Basso, Kumar, & Malow, 2009; Rippeth et al., 2004). Domains commonly affected include executive functioning, information processing, motor functioning, attention, learning, and memory (Al-Zahrani & Elsayed, 2009; I. Grant & Heaton, 1990; Heaton et al., 1995). Antiretroviral therapy (ART) can significantly reduce NCI symptoms but mild forms persist in a large proportion of PLWHA who are also on ART (Foley et al., 2008; Joska, Gouse, Paul, Stein, & Flisher, 2010a).

NCI has been shown to demonstrate a significant association with sex- and drug-related risk behaviors (Chander et al., 2009), and a negative association with HAART adherence (Anand et al., 2010; Hinkin, Castellon, Durvasula, Hardy et al., 2002; Lovejoy & Suhr, 2009). Since HIV infection is spread primarily by risk behaviors, and successful HIV treatment depends on optimal adherence, improving antiretroviral adherence and reducing HIV transmission risk behaviors is the main focus of most interventions targeting drug-involved PLWHA.

Such intervention sessions typically place a high demand on various cognitive domains including memory, learning, and attention. Some interventions take into account the possibility of NCI in the target populations and try to tailor intervention content delivery accordingly (e.g. the use of cognitive remediation strategies; Copenhagen, Avants, Warburton, & Margolin, 2003).

Although associations have been established between NCI and adherence and between NCI and HIV risk behavior, it is not known how NCI may influence the treatment outcomes of these two very important variables in PLWHA. The purpose of the current study was to assess the relationship between NCI and treatment outcomes in a sample of drug-involved PLWHA who participated in the Holistic Health for HIV intervention (3H+; Copenhagen et al., 2011) in New Haven, Connecticut. The 3H+ is a behavioral intervention aimed at reducing HIV risk and improving medication adherence in HIV-infected IDUs. It was adapted from an evidence-based intervention - the Holistic Health Recovery Program for HIV+ drug users (HHRP+; Margolin et al. 2003). We hypothesized that subjects with greater NCI would demonstrate less improvement in knowledge, motivation and behavior skills relating to medication adherence and sex- and drug- related risk behavior following the 3H+ intervention.

METHOD

Design

This was a retrospective secondary analysis for a sample of drug-involved PLWHA who participated in the Holistic Health for HIV intervention (3H+; Copenhagen et al., 2011) in New Haven, Connecticut. Variables for HIV-related drug- and sex-risk behavior had been created for the primary study and NCI was assessed using the neuropsychological impairment scale (NIS; O'Donnell et al 1983).

Sample

HIV infected individuals who were on prescribed antiretroviral medication and who were receiving methadone maintenance therapy participated in the 3H+ intervention. Inclusion criteria included meeting DSM-IV opioid dependence criteria and self-reported HIV risk behavior. For the purpose of the study, risk behavior was defined as having used IV drugs or having unprotected sex in the past month. Participants were 64% African American, 18% Caucasian, and 15% Latino. 46% of them had contracted HIV through drug related behaviors and almost 80% had an annual income of less than \$10,000. 39 subjects enrolled, out of which 10 dropped out immediately after the pre-intervention assessment. There was no difference in demographics between those who dropped out and those who remained in the study; however, drop outs reported higher frequency of heroin use and less self-efficacy about sex risk reduction (Copenhagen et al., 2011). All 29 remaining individuals were available for least one intervention session and 21 subjects participated in the post-intervention assessment. Participants were generally long-term drug users, reporting both cocaine and heroin use and an average of 4 sexual partners in the last month. Participants were reimbursed for the time required to complete the assessments.

Measures

The Neuropsychological impairment scale (NIS; O'Donnell, Reynolds & De Soto, 1983) is a brief, self-report measure used to rapidly assess NCI. The NIS is generally used as a screening instrument in clinical settings and not as a diagnostic tool for NCI. Although clinical diagnosis requires the use of a more comprehensive assessment battery of instruments, recent studies have stressed the need for rapid screening tools for neurocognitive deficits (Schouten et al., 2011). The NIS has been shown to have strong

sensitivity (.91) and specificity (.76) in a sample of neuropsychiatric patients using the Halstead Impairment Index which is a standard, more comprehensive neuropsychological battery (O'Donnell, Reynolds & De Soto, 1984; Avants et al., 1997). In a study using the NIS to determine whether cocaine dependent patients differed by HIV status based on self-awareness of cognitive impairment, HIV positive subjects were more likely to show impairment on several NIS subscales (Avants et al., 1997).

The NIS is composed of 95 items with point scale coded responses. These responses are used to compute 7 subscale scores and 3 summary scores. The subscales assess Critical Items (CRIT; this assesses the patient's history of neurological illness or injury), Cognitive Efficiency (COG), Attention (ATT), Memory (MEM), Frustration Tolerance (FRU), Learning Verbal (LV), and Academic Skills (ACD). These scores provide an indication of impairment for the respective cognitive domains. Assessment of overall cognitive functioning is provided by the summary scores which are the Global Measure of Impairment (GMI), Total Items Circled (TIC), and Symptom Intensity Measure (SIM). Generally, high levels in any of these scores are an indication of NCI.

There are also validity checks which provide a background for the interpretation of the other scores. Defensiveness (DEF) is an indication of the test takers attitude, Affective Disturbance (AFF) is an indication of emotional state of the subject at the time of the test, and Response Inconsistency (INC) identifies inconsistent response pairs. A 4 point scale (0: Not at all; 3: extremely) was used to code responses. For each subscale, sums of the point scale scores were totaled and then transformed to T scores which were used in the current analysis as a continuous variable. NIS scores <30T were considered low, scores >30T and <50T were considered average, a high score was >50T and < 60T, and any score above 60T was considered very high.

Measures based on the Information, Motivation, and Behavior Skills (IMB; Fisher et al. 1994; Fisher et al., 2008) model were used to assess medication adherence and HIV risk reduction behavior. These measures have been used in prior NIH-funded studies and show good psychometric properties (e.g., Copenhaver et al., 2011; Copenhaver et al., 2009).

Variables

NIS measurements comprising 7 impairment subscales, 3 validity scores, and 3 summary scores were taken at baseline and post-intervention assessment points. Constructs for medication adherence and HIV related risk behavior were created for the primary study based on the IMB model (Copenhaver et al., 2011; Copenhaver et al., 2009). These were measured at baseline, post-intervention, and at a three month follow-up session. Change in treatment outcome was assessed by computing the percentage difference between baseline and post-intervention scores for adherence and HIV risk Behavior. Examples of questions used to compute the construct for adherence Information were 'what should you do if you develop side effects?' and 'what should you do if you cannot remember how frequently to take your medication?' Examples of personal and social Motivation items pertaining to drug use are 'in the next 6 months do you plan (intend) to stop using heroine completely?' and 'how important is being drug free to most of the people in your "social network"?'. Examples of Behavioral Skills self efficacy and reported Behavior items pertaining to sexual behavior are 'how confident are you that you would bring up the issue of condoms or safer sex in a conversation when sober' and 'how many sexual partners have you had in the past 30 days?'

Intervention

The 3H+ intervention is a theory-driven, manual-guided behavioral HIV risk reduction intervention consisting of four 45-minute weekly psycho-educational style group meetings led by two graduate-level trained facilitators (Copenhaver et al. 2011). The intervention content focuses on HIV related drug- and sex- risk reduction and medication adherence (Table 1). The 3H+ intervention employed cognitive remediation strategies designed to assist subjects who have moderate cognitive difficulties. These involved multi-modal (verbal, visual, and experiential) presentation of material, learning by doing (e.g. the use of role playing), structure and consistency (sessions were carried out at the same time and location every week), using simple language and reviewing material frequently.

Data Analysis

Baseline (n=36) and post-intervention (n=21) data were included in the secondary analysis. A cross sectional design was used to separately assess associations between Adherence and HIV risk Behavior with neurocognitive status at baseline and post intervention, while a longitudinal design was used to assess the association between change in Adherence and risk Behavior (from baseline to post intervention) with neurocognitive status. First, simple correlations were carried out between all NIS scores and IMB construct scores (baseline, post intervention, and change from baseline to post intervention). This was done in order to narrow down the number of NIS scores such that only scores that were significant predictors of treatment outcomes were included in the final regression models. This was due to the limited sample size and large number of variables of interest. P values were set at $<.05$ and SPSS software was used for all statistical analyses described below.

RESULTS

There was no difference across participants between NIS scores at baseline and post-intervention; thus, the baseline NIS scores were used for this analysis. Mean NIS scores (Table 2) ranged from approximately 40T on the defensiveness subscale to 60T for critical items and cognitive efficiency subscales. Tables 3, 4 and 5 show the coefficient of determination (R^2 ; i.e. how much of the variance in each of the constructs was explained by their respective predictors). At baseline, Critical items, Cognitive efficiency, Frustration tolerance, Memory, and Global measure of impairment were negatively associated with Adherence Self-efficacy while Response inconsistency and Affective disturbance were significantly associated with Adherence Motivation post intervention. 25.1% and 24.8% of the variance in adherence self-efficacy and adherence motivation respectively was explained by the combination of their respective predictors. There was no significant association between any of the risk behavior constructs and NIS scores at baseline.

At post intervention, drug use social Motivation was negatively associated with Response inconsistency while drug use Self-efficacy was found to be significantly associated with Learning verbal, Critical items, Memory, Defensiveness and Academic skills. In combination, the respective predictors accounted for 24.4% and 81.3% respectively of the variance in drug use social Motivation and drug use Self-efficacy. Reported drug use frequency was positively associated with Critical items and 21% of the variance of reported drug use frequency was explained by Critical items.

Improvement in adherence Motivation from baseline to post-intervention was negatively associated with Memory and Response inconsistency and together these explained 27.2% of the variance in change in adherence Motivation whereas Symptom intensity measure was negatively associated with increased social Motivation pertaining to drug use behavior,

explaining 24.6% of the variance. Results of the various regression models, with all the significant predictors included in the analysis, are presented in table 6.

DISCUSSION

The 3H+ intervention produced significant improvements in adherence, sex behavior self-efficacy, and in reported sex behavior and drug use from pre-intervention to post-intervention (Copenhaver et al. 2011). This secondary analysis enables the results of the intervention to be viewed in light of NCI characteristics of the participants, and suggests the degree to which NCI may have influenced their participation in the intervention.

Consistent with other studies with this target population of HIV+ drug users (Margolin et al 2002; Del Pesce, 1993; Martin et al. 2007), NCI was evident in this group of participants, as indicated by most average scores within the 50–60T range. Higher levels of NCI were associated with poorer adherence and higher levels of risk behavior, as is also consistent with several prior studies (Hinkin, Castellon, Durvasula, Lam et al., 2002; Hinkin et al., 2004; Martin et al. 2007). To our knowledge, this is the first study to assess the potential association between NCI and medication adherence and risk reduction intervention outcomes in drug-using PLWH. Following the intervention, improvements in adherence and drug risk reduction outcomes were negatively associated with NCI. Although most regression models did not reach conventional levels of significance – owing to the inclusion of a relatively small sample size – the moderately large R^2 values that were observed suggest that additional significant associations may have been observed given a larger sample size. The mean value for Defensiveness suggests that participants had a positive and open attitude in completing the assessment. The mean Affective disturbance score suggested some degree of emotional strain at the time testing which was not surprising considering the low socioeconomic status of the majority of our sample.

There were more NCI correlates – global and specific - with Behavioral Skills constructs and, interestingly, this was the area where significant changes were observed following the 3H+ intervention (Copenhaver et al., 2011). Another interesting observation was that the 3H+ intervention did not produce any changes in the Information constructs (Copenhaver et al., 2011) and there were no NCI correlates with any of the Information constructs or change in information from baseline to post intervention. It was surprising, however, to find that although the 3H+ intervention did not produce any significant overall improvements in Motivation constructs (Copenhaver et al., 2011), changes in adherence Motivation and drug use social Motivation were negatively predicted by Memory and Symptom intensity measure respectively.

NCI appears to play a significant role in how drug-involved PLWHA respond to secondary HIV risk reduction interventions targeting adherence and risk behavior. These interventions typically place a high demand on several cognitive domains such as memory, learning, and attention and NCI may be a potential confounding variable with regard to treatment outcomes.

The results of this study should be viewed in light of a number of limitations. First, the sample size included in this secondary analysis was relatively small. It was not sufficiently large to generate the statistical power to examine all variables of interest. The observed R^2 values, however, suggest that the findings are worthy of follow-up investigations. Secondly, the NIS, although a very user-friendly and convenient tool for difficult-to-reach populations such as injection drug users, it does not provide a comprehensive assessment of NCI and does not measure all possible cognitive domains although it has been shown to correlate strongly with a full neurocognitive battery (Avants et al., 2007). Thirdly, scores of

adherence and risk behavior are highly correlated with one another, as are scores on different NIS subscales, and we were not able to control for this due to the small sample size. It is possible that, with a larger sample, a multivariate analysis of covariance could be carried out which would allow us to control for such associations as well as various baseline characteristics. Fourthly, all assessments were based on self-report, which carries with it inherent limitations, especially because the study sought to examine mostly socially unacceptable behaviors. This may have been moderated, however, by the use of ACASI system, which provided participants with a high level of privacy in addition to the assurance of anonymity, and there were no significant signs of defensive or dishonest response sets. Finally, subjects with poor scores on the validity checks could have been excluded from this analysis for more accurate interpretation of results. Such an approach, however, would have further reduced statistical power due to a relatively small sample size.

While the cognitive remediation strategies employed in the 3H+ intervention may have moderated the influence of NCI, this specific effect was not measured, and thus we are not aware of how the incorporation of cognitive remediation strategies may have affected participants' outcomes. If cognitive remediation was indeed influential, however, the outcomes of this study would have been expected to be even more extreme since NCI was still found to predict treatment outcomes. That is, in the absence of cognitive remediation strategies, one would have expected the intervention to have been more challenging to the participants, and the influence of NCI would therefore have been even more evident.

CONCLUSION

Results of this study suggest that more attention should be paid to screening for NCI in this population, and potentially accommodating mild to moderate levels of NCI in the delivery of interventions as implied in prior work (Copenhaver et al., 2003). This is particularly important in the post-ART era where NCI symptoms are mostly mild and can very easily go undetected, be mistaken for psychological distress symptoms, or be mistaken for other effects of active drug use such as hangovers or being 'high'. Controlling for NCI in studies with this population may also allow a more accurate interpretation of results. Future studies should utilize a larger sample, use more comprehensive and sensitive assessment instruments for NCI, and specifically examine the contribution of cognitive remediation strategies. This would be consistent with several current NIH initiatives addressing this target population (e.g. NIDA RFA: PA-07-307; Drug Abuse aspects of HIV/AIDS). In addition, it will be important to assess the associations of NCI and intervention outcome variables at follow-up which was not possible in the present study due to limited sample size. Treatment drop out and relapse to drug use are common following behavioral interventions and it would be useful to determine the extent to which neurocognitive impairment plays a role in these negative events.

Relatively high scores on Affective disturbance observed were not unexpected in this sample considering the social and economic challenges faced by this population (Hendricks et al., 2010). This suggests, however, that those who administer neuropsychological tests may need to avoid activities that could add any more emotional strain to participants coinciding with test taking as this could potentially affect the reliability of test results. Although several behavioral risk reduction approaches such as the 3H+ intervention have been shown to be efficacious in this target population of HIV+ drug users, such interventions may not be the first line of treatment for patients with cognitive difficulties, and it may still be necessary to explore other intervention approaches to improve adherence and reduce risk behavior in drug involved PLWHA. Substance use treatment such as methadone maintenance to address drug risk behavior, and the use of medication adherence aids such as pill boxes have, of course, been shown to play a helpful role. This study, as well

as previous studies, suggests that there could be a significant subgroup of drug-involved PLWHA defined by neurocognitive impairment. Recognizing this and tailoring treatment to meet their needs may be a critical aspect of improving interventions targeting drug-involved PLWHA.

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Table 1

Outline of the CHRP+ HIV risk reduction and antiretroviral adherence intervention

Group Topic	Information, Motivation, & Skills Taught
Active Health Care Participation	Understanding HIV And Your Immune System, Strategies for Improving Health, Developing a Partnership With Health Care Providers, and Enhancing Antiretroviral Adherence Skills
Reducing Drug-related Risk	Identifying Drug-Related HIV-Risks, Learning About Proper Needle Cleaning, and Managing Drug Cravings
Risk Reduction With Male and Female Condoms	Identifying Sex-Related HIV Risks, and Learning About Latex Products and Their Correct Use
Negotiating Risk Reduction With Partners	Negotiating Use of Latex, and Communicating About Sex- and Drug-Related HIV-Risk

Table 2

Summary of NIS scores

Predictor	Min	Max	Mean	SD
Validity Scores				
• Response Inconsistency	32.00	68.00	51.78	8.34
• Defensiveness Scale	31.00	56.00	40.08	6.26
• Affective Disturbance	32.00	72.00	56.75	11.56
Summary Scores				
• Global Measure	30.00	80.00	57.58	13.89
• Total Items Circled	30.00	80.00	55.51	16.75
• Symptom Intensity Measure	33.00	77.00	56.23	11.49
Impairment Subscales				
• Critical Items	38.00	80.00	57.97	13.18
• Cognitive Efficiency	35.00	76.00	57.97	12.78
• Attention	30.00	76.00	53.97	13.52
• Memory	30.00	75.00	56.06	12.46
• Frustration Tolerance	33.00	76.00	55.50	13.24
• Learning-Verbal	37.00	80.00	56.42	13.49
• Academic Skills	32.00	74.00	54.86	12.96

Summary of NIS scores (pre intervention) n=36.

Table 3

Significant predictors (NIS scores) of adherence at baseline and post intervention.

Predictor	Adherence Self Efficacy (pre intervention) n=36 (Pearson correlation R)	Adherence Motivation (post intervention) n=21 (Pearson correlation R)
Validity Scores		
-Response Inconsistency	-.088	-.444 *
-Defensive scale	.246	.003
-Affective Disturbance	-.295	-.434 *
Summary Scores		
- Global Measure	-.362 *	-.249
- Total Items Circled	-.394	-.135
- Symptom Intensity Measure	-.075	-.177
Impairment Subscales		
- Critical Items	-.333 *	-.110
- Cognitive Efficiency	-.395 *	-.325
- Attention	-.287	-.326
- Memory	-.351 *	-.184
- Frustration Tolerance	-.339 *	-.284
- Learning-Verbal	-.283	.001
- Academic Skills	-.265	-.038
Total Variance explained R² (by combined significant predictors)	25.1%	24.8%

* p<.05;

** p<.01;

*** p<.001

Table 4

Significant predictors (NIS scores) of risk behavior at post intervention.

Predictor	Drug use self- efficacy (post intervention) n=21 (Pearson correlation R)	Drug use Social motivation (post intervention) n=21 (Pearson correlation R)	Drug Use reported behavior frequency (post intervention) n=21 (Pearson correlation R)
Validity Scores			
Response Inconsistency	-.294	-.419 *	.101
Defensive scale	.519 *	.024	.009
Affective Disturbance	-.248	-.230	.217
Summary Scores			
- Global Measure	-.475 *	-.265	.322
- Total Items Circled	-.598 **	-.246	.460 *
- Symptom Intensity Measure	-.090	-.258	.159
Impairment Subscales			
- Critical Items	-.668 ***	-.242	.459 *
- Cognitive Efficiency	-.259	-.283	.354
- Attention	-.354	-.223	.265
- Memory	-.420 *	-.233	.168
- Frustration Tolerance	-.353	.003	.177
- Learning-Verbal	-.513 *	-.473 *	.311
- Academic Skills	-.448 *	-.206	.240
Total Variance explained R² (by combined significant predictors)	81.3% *	24.4%	23.7%

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

Table 5

Significant predictors (NIS scores) for change in outcome from pre to post

Predictor	Adherence motivation (change) n=21 (Pearson correlation R)	Drug use social motivation (change) n=21 (Pearson correlation R)
Validity Scores • Response Inconsistency	−0.465 *	−.475 *
Summary Scores • Symptom Intensity Measure	−.066	−0.496 *
Impairment Subscales • Memory	−0.489 *	−.227
Total Variance explained R² (by combined significant predictors)	27.2%	31.1% *

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

Table 6

Regression Model Summaries (with all significant predictors included in the model).

Model	Dependent variable	Predictors	R	R ²	Sig
1	Adherence Self-efficacy(pre)	CRIT,COG,FRU,MEM,GMI	.501	.251	.106
2	Adherence Motivation (post)	AFF, INC	.498	.248	.077
3	Drug use Social motivation (post)	LV, INC	.494	.244	.081
4	Drug use Self-efficacy (post)	LV, CRIT, MEM, DEF, ACD, GMI	.813	.661	.009
5	Drug use Reported behavior frequency(post)	CRIT	-.487	.237	.088
6	Adherence Motivation (pre-post)	MEM, INC	.522	.272	.057
7	Drug use Social motivation (pre- post)	SIM	.557	.311	.035