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Depressive symptoms, quality of life, and neuropsychological performance in HIV/AIDS: The impact of gender and injection drug use

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Limited attention has been paid to the potential impact of gender and injection drug use (IDU) on mood, quality of life, and neuropsychological performance in human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Several studies that describe the natural history of HIV/AIDS in terms of mental health and neuropsychological ability have focused solely on men or have excluded injection drug users. Women and injection drug users are two groups for whom the incidence of HIV infection is increasing. Additionally, the National Academy of Sciences recently recommended that studies concerned with health-related research include males and females, and that researchers analyze their data for gender differences. The goals of the current study were to investigate possible relationships between HIV and IDU status and depressive symptoms, quality of life, and neuropsychological performance in women and men matched for age, race, and education. Overall, women reported more depressive symptoms than men, and this gender difference was most evident in women who were both infected with HIV and who were also injection drug users. Women and HIV-infected individuals reported the poorest quality of life scores. Women outperformed men on a measure of verbal memory and HIV$^-$ participants outperformed HIV$^+$ participants on a measure of perceptual speed. Finally, gender and HIV status interacted such that uninfected women performed the best, and infected men performed the worst, on a test of verbal memory. A better understanding of how men and women with different drug use profiles respond to HIV/AIDS may substantially improve survival, as well as aspects of daily functioning, of affected individuals. Thus, further study and development of treatment protocols targeted at including women and IDU are needed. *Journal of NeuroVirology* (2005) **11,** 138–143.

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Depression, poor quality of life, and cognitive impairment are known consequences of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). In addition to influencing the daily lives of patients, their friends and families, these outcomes are associated with medication noncompliance, morbidity, and mortality (Evans *et al*, 2002; Farinpour *et al*, 2003; Ickovics *et al*, 2001; Jacobson *et al*, 2003; Starace *et al*, 2002).

Several studies that describe the natural history of HIV/AIDS in terms of mental health have focused on men, and/or have excluded injection drug users (Farinpor *et al*, 2003; Lyketsos *et al*, 1996; Morrison *et al*, 2002; Vazquez-Justo *et al*, 2003; but see McClure

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et al, 1996; Turner *et al*, 2003). Furthermore, when women were included their data were often compared to historical data collected from men (Evans *et al*, 2002; McDonnell *et al*, 2000), or were not analyzed according to gender (Sherbourne *et al*, 2000). Women and injection drug users are groups for whom the incidence of HIV infection is increasing (Ickovics and Rodin, 1992). Therefore, studies designed to investigate the impact of HIV/AIDS on depression, quality of life, and cognition in women and drug abusers are needed.

The National Academy of Sciences recently reported that "Gender Matters," and went on to recommend that studies concerned with health-related research include both males and females, and also analyze their data for gender differences (Wizemann and Pardue, 2001). The goals of the current study were to investigate relationships between HIV and injection drug use (IDU) status with depressive symptoms, quality of life, and neuropsychological performance in women and men matched for age, race, and education.

Results

Demographic characteristics

The majority (95%) of participants classified themselves as African Americans. Approximately half of the study cohort was HIV^+ and/or IDU^+ (Table 1a). Men and women were matched according to their HIV and IDU status (Table 1b). Of the IDU^+ participants, a combination of heroin only, cocaine only, or speedball injections were reported (Table 2). Among HIV^+ participants, fewer than half were taking (HAART) when tested (40% women and 35% men). Neither age (male mean = 44.8 years, female mean = 42.2 years) nor education (male mean = 11.8 years, female mean = 11.7 years) differed between men and women who participated in the current study (P values > .05). In terms of drug use patterns at study enrollment other than IDU, a majority of participants reported cigarette (85%) and alcohol (62%) use, and a minority reported smoking marijuana (22%), smoking heroin (2%), or snorting cocaine (2%).

Table 1a General characteristics of the study cohort ($n = 61$)

Variable	*n (%)*
Gender	
Male	31 (51)
Female	30 (49)
Race	
African American	58 (95)
Caucasian	3 (5)
HIV status	
HIV^+	27 (44)
HIV^-	34 (56)
IDU status	
IDU^+	32 (52)
IDU^-	29 (48)
Education	
≥12th Grade	40 (66)
<12th Grade	21 (34)

Table 1b Number of men and women who were matched according to HIV and IDU status ($n = 61$)

	Male	*Females*
HIV^-IDU^-	9	8
HIV^+IDU^-	8	4
HIV^-IDU^+	5	12
HIV^+IDU^+	9	6

Depression

Overall, women (mean Center for Epidemiologic studies Depression Scale [CESD] = 20.96) reported more depressive symptoms than men (mean CESD = 15.93) ($F(1, 59) = 4.13$, $P < .05$; Figure 1a). Additionally, an interaction between HIV^+ and IDU^+ was observed for CESD scores ($F(3, 57) = 6.45$, $P < .05$) where HIV^+IDU^+ individuals reported the most depressive symptoms (Figure 1b). Depressive symptoms were reported most often by HIV-infected women who were also injection drug users (83% obtained a CESD score ≥ 16). Due to the limited sample size, this failed to reach statistical significance ($\chi^2(9) = 7.18$, $P > .05$). No other group differences were observed for CESD scores (P values > .05).

Quality of life

Women ($F(1, 58) = 4.10$, $P < .05$) and HIV^+ participants ($F(1, 58) = 12.43$, $P < .005$) scored lower, indicating a poorer quality of life, on the physical health summary (PHS) score of the Medical Outcomes Study HIV Health Survey (MOS-HIV) (Figure 2a,b).

In addition to the physical health subscale of the MOS-HIV, HIV^+ participants also scored worse on the mental health summary (MHS) subscale of the MOS-HIV ($F(1, 59) = 7.12$, $P < .05$; Figure 3). No other group differences were observed for the MOS-HIV scores (P values > .05).

Both the PHS ($F(3, 57) = 11.48$, $P < .0005$) and the MHS ($F(2, 58) = 14.44$, $P < .0005$) scores of the MOS-HIV covaried significantly with CESD scores for participants. In general, for every 1 point increase

Table 2 Characteristics of the IDU^+ participants by injection drug use patterns ($n = 32$)

	Male IDU^+	*Female IDU^+*
Heroin	7	7
Cocaine	2	5
Speedball	5	6

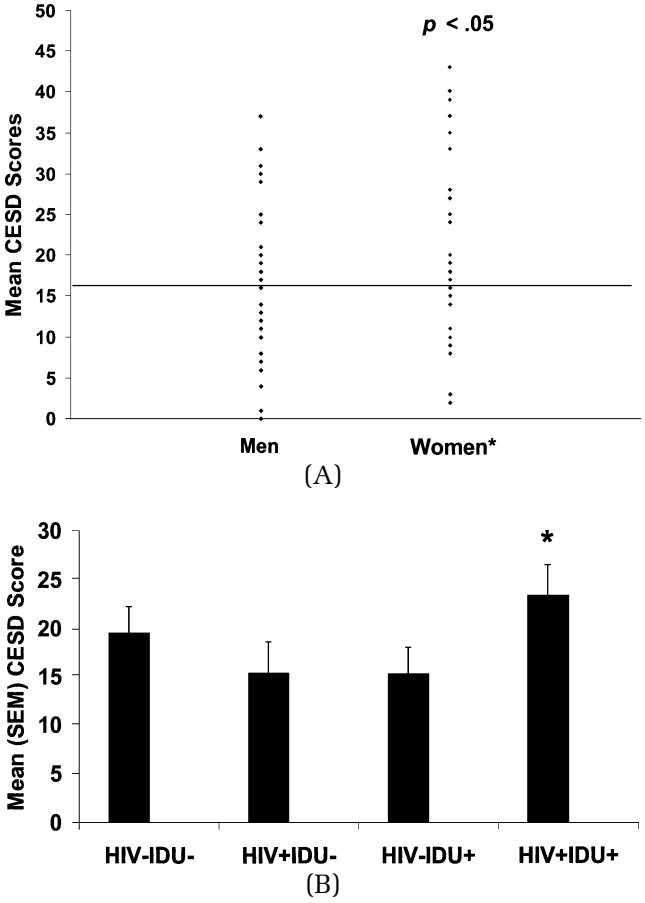

Figure 1 (**A**) CESD scores for men and women. Scores ≥ 16 indicate depression. An asterisk (*) indicates that women (mean CESD = 20.97) reported significantly more depressive symptoms than men (mean CESD = 15.94). (**B**) Mean (SEM) CESD score. Scores ≥16 indicate depression. An asterisk (*) indicates that HIV$^+$IDU$^+$ participants reported significantly more depressive symptoms (mean CESD = 23.27) than individuals in the other groups (mean CESD HIV$^-$IDU$^-$ = 19.47; mean CESD HIV$^+$IDU$^-$ = 15.33; mean CESD HIV$^-$IDU$^+$ = 15.24).

in CESD, roughly a half of a point decrease in PHS and MHS was observed. This relationship between depressive symptoms and poor quality of life was evident regardless of gender or HIV or IDU status.

Neuropsychological assessment

Univariate analyses revealed that women outperformed men on a delayed verbal memory test ($F(1, 51) = 11.0$, $P < .005$, and HIV$^-$ participants outperformed HIV$^+$ participants on a measure of perceptual

Table 3 Mean (SEM) scores on neuropsychological tests

Gender	♀	♂
HVLT% recall	81.34	57.15
	(3.28)	(6.97)
HIV	−	+
Identical pictures	18.81	13.73
	(1.12)	(0.93)

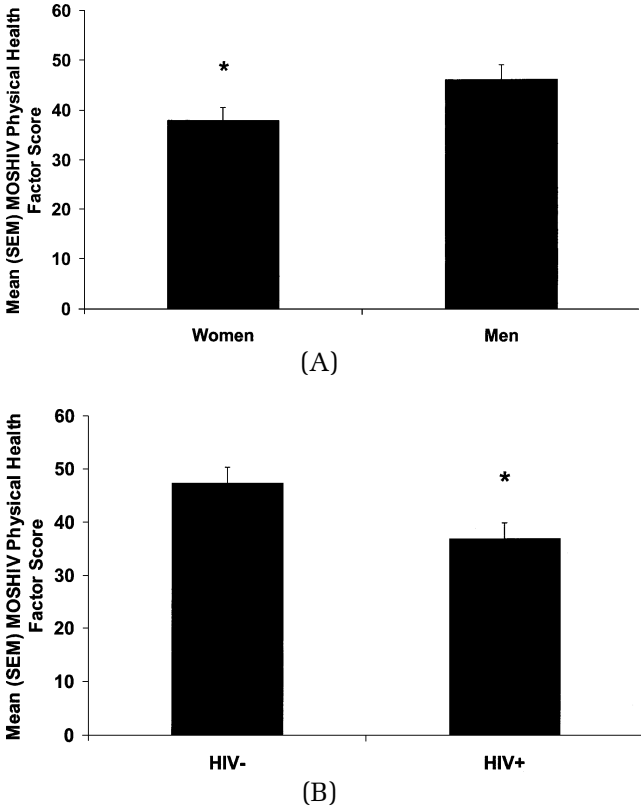

Figure 2 (**A**) Mean (SEM) MOS-HIV Physical Health Factor score. Higher scores represent better physical health-related quality of life. An asterisk (*) indicates that women exhibited poorer physical health-related quality of life (mean = 37.98) compared to men (mean = 46.10). (**B**) Mean (SEM) MOS-HIV physical health factor score. Higher scores represent better physical health-related quality of life. An asterisk (*) indicates that HIV$^+$ participants exhibited poorer physical health-related quality of life (mean = 36.77) compared to HIV$^-$ participants (mean = 47.30).

speed ($F(1, 51) = 10.82$, $P < .005$; Table 3). Multivariate analyses revealed a significant interaction between gender and HIV status for verbal memory, where HIV$^-$ women performed the best and HIV$^+$ men performed the worst, on a delayed verbal recall test ($F(3, 49) = 4.86$, $P < .05$; Table 4). No other group differences or interactions for neuropsychological performance were observed (all P values > .05).

Discussion

Our data illustrate that depressive symptoms are common in men (45% CESD ≥ 16) and women (63%

Table 4 Mean (SEM) scores on a verbal memory test that revealed significant interactions between gender and HIV status

Gender × HIV	Female HIV$^-$	Female HIV$^+$	Male HIV$^-$	Male HIV$^+$
HVLT % recall	83.65	76.21	59.0	55.6
	(4.2)	(4.7)	(10.7)	(9.5)

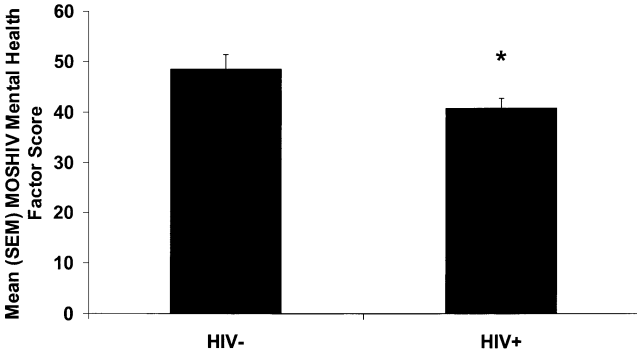

Figure 3 Mean (SEM) MOS-HIV Mental Health Factor score. Higher scores represent better mental health-related quality of life. An asterisk (*) indicates that HIV^+ participants exhibited poorer mental health–related quality of life (mean = 40.76) compared to HIV^- participants (mean = 48.52).

CESD $\geq$ 16) from a predominantly middle-aged, low-income, African American cohort matched for HIV and IDU status. Importantly, HIV^-IDU^- controls were recruited from the same socioeconomic and racial group, strengthening our interpretation that HIV and IDU directly impact affective disorders in this group. A previous study of women with lower socioeconomic status reported similarly high rates of depressive symptoms (Richardson *et al*, 2001). Previous studies of HIV-infected individuals indicate that depression is associated with morbidity, mortality (Ickovics *et al*, 2001; Farinpour *et al*, 2003), and noncompliance with medication (Selnes, 2002). Among investigations of affective disorders in HIV-infected populations that have included women, active injection drug users have largely been omitted from participation. Conversely, studies of depression that have included both HIV and IDU participants have, for the most part, excluded women (but see McClure *et al*, 1996 and Rabkin *et al*, 1997). Depressive symptoms were most pronounced in women who were both HIV^+ and IDU^+; however, this difference failed to reach statistical significance. In light of the potential clinical significance of these results, future studies should be conducted that have adequate power to uncover such potentially important sex differences in populations affected by HIV/AIDS and IDU.

Measures of quality of life are important to assess the efficacy of, and need for, HIV/AIDS patient services and treatment (Hays *et al*, 2000). Similar to depression, poor quality of life is also associated with morbidity and mortality in patients with advanced HIV disease (Jacobson *et al*, 2003). We observed decreased quality of life concerning both mental and physical health in HIV-infected participants (Hays *et al*, 2000; McDonnell *et al*, 2000). We also observed poorer PHS in women compared to men, regardless of their HIV or IDU status. Past investigations that did not report similar gender differences compared women's results to historical data collected from men (McDonnell *et al*, 2000), or recruited women who did not resemble those in the current study in terms of race, age, and education (Hays *et al*, 2000).

Finally, IDU subjects have not traditionally been included in neuropsychological studies of HIV-infected individuals because drug use may confound the effects of HIV on cognitive task performance (but see Margolin *et al*, 2002). In the current study, men and women were matched for HIV and IDU status while controlling for education level and age. Women recalled more items on a verbal memory recall task, and HIV^- participants performed better on a task that measures perceptual speed than men or HIV-infected individuals, respectively. These results are consistent with a large literature regarding gender differences in cognitive performance for the general population (Sherwin, 2003a, 2003b), and the impact of HIV/AIDS on neuropsychological performance (Selnes *et al*, 1995). Gender and HIV status interacted in significant ways, such that HIV-infected men were at a disadvantage for tasks that included components of verbal memory. This pattern of results may have implications for addressing medication noncompliance (Avants *et al*, 2001; Cook *et al*, 2002; Selnes, 2002; Turner *et al*, 2003) and general functioning. Although IDU status did not significantly impact neuropsychological test performance in the present study, previous work indicates that cocaine and heroin use are associated with impaired executive function (Lyvers and Yakimoff, 2003; Matochik *et al*, 2003; Rippeth *et al*, 2004). Future studies should continue to consider the independent, and potentially additive, influence of HIV and IDU on cognition.

Gender, HIV and IDU status are differentially associated with depressive symptoms, quality of life, and cognition. Such individualized responses to the natural history of HIV/AIDS are underappreciated because women and IDU participants have not always been included in studies of HIV/AIDS. A better understanding of individualized responses to HIV/AIDS and drug abuse may substantially improve survival and aspects of daily life of affected individuals, thus further study and development of treatment protocols aimed at specific at-risk populations are needed.

Study limitations and future directions

Limitations of the current study include having no information regarding viral load or CD4 counts for HIV-infected participants. Additionally, although significant effects of sex were observed for depression, quality of life, and verbal memory, we were unable to obtain sex steroids from participants. Finally, although the IDU^+ participants fulfilled the criteria of drug abuse needed to be included in this category for the current study, a detailed drug use history was unavailable for participants. These pieces of information may be critical in understanding the mechanisms underlying the different natural histories of IDU and HIV/AIDS in men and women, and future studies will benefit from including these measures.

Methods

Participants
A total of 61 men and women were recruited from an on-going study of endocrine health and metabolism in a drug abusing population (SHINE Study, The Johns Hopkins School of Medicine, Baltimore MD) to participate in the current cross-sectional investigation. HIV and IDU status were determined via questionnaire responses, and then verified with information obtained from medical records. IDU^+ was defined as injecting cocaine, heroin, a combination of cocaine and heroin (speedball), and/or street methadone at least 3 times/week for a minimum of 3 months. IDU^- was defined as abstaining from injecting any of these drugs for at least 3 years prior to enrollment. Participation was voluntary and confidential. Study procedures lasted approximately 1 h, and participants were compensated with $10 for their time. The Johns Hopkins Institutional Review Board approved all study procedures, and participants provided written, informed consent prior to their enrollment.

CESD
The CESD is a screening instrument that contains 20 questions pertaining to depressive symptoms during the past week. Participant responses to each question range from 0 to 3. Mean CESD scores $\geq$ 16 indicate depression.

MOS-HIV
The MOS-HIV is a 35-question survey designed to assess 10 dimensions of quality of life in HIV^+ individuals (Wu *et al*, 1991, 1997). For the MOS-HIV responses, scores were transformed to a 100-point scale, with 0 being the lowest score possible and 100 being the highest score possible. Two summary quality of life scores, PHS and MHS, were then calculated from the 10 quality of life dimension scores as described by Revicki *et al* (1998). The PHS score deals with self-reported physical function, pain, role and social function, and health perception. The MHS score deals primarily with mental health and distress, quality of life, cognition, and energy level. Routinely, both summary scores are standardized where the mean score is 50 with a standard deviation of 10 (Jacobson *et al*, 2003). Higher scores represent better quality of life.

Cognitive Test Battery
The National Adult Reading Test (NART) is a measure of intelligence where subjects are asked to read aloud from a list of words that do not follow standard phonetic rules for pronunciation. The Digit Span (Forward and Backward) Test (WAIS-III) measures working memory by requiring subjects to maintain a sequence of digits in their memory and then report the sequence, either in the original sequence or in reverse order, back to the experimenter. The Hopkins Verbal Learning Task (HVLT) is a measure of verbal learning and memory where subjects are required to learn and recall, immediately and following a 20-min delay, and also to recognize a list of target words. The Rey Complex Figure (RCF) Copy with Delayed Recall measures visuoconstruction and visual memory and requires subjects to copy a complex figure, immediately recall the figure, and then recall the figure again following a 20-min delay. The Verbal Fluency Task measures aspects of executive function by requiring subjects to generate lists of words that start with a specific letter. The Trail Making Tests A and B measure divided attention, visuospatial tracking, and perceptual motor speed. These timed tests require participants to connect sequences of number, or numbers and letters. Fine motor control is measured with the Identical Pictures Task, where subjects are required to quickly match a series of items from lists of distracters.

Statistical analyses
Descriptive statistics and *t* tests were generated to examine demographic characteristics and group differences of participants for continuous descriptive variables. Chi-square analyses were conducted when examining bivariate variables. Group comparisons to consider the independent predictor variables of gender and HIV and IDU status for depression, quality of life, and neuropsychological test scores were assessed, while controlling for effects of age, race, and education, with the General Linear Model (GLM) procedure. Relationships between depression and quality of life were examined for all of the groups with the GLM by examining CESD scores while covarying PHS and MHS scores.

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