Fatigue in HIV/AIDS is Associated With Depression and Subjective Neurocognitive Complaints but not Neuropsychological Functioning

Colleen P. Millikin1, Sean B. Rourke1,2, Mark H. Halman1,2, and Christopher Power3
1Mental Health Service and Inner City Health Research Unit, St. Michael’s Hospital, Toronto, Ont., Canada, 2Department of Psychiatry, University of Toronto, Toronto, Ont., Canada, and 3Departments of Clinical Neurosciences, Microbiology & Infectious Diseases and Neuroscience Research Group, University of Calgary, Calgary, Alta., Canada

ABSTRACT

Fatigue and depressive symptoms are common in HIV-infection. The relationship between these symptoms and neuropsychological functioning is poorly understood, particularly in symptomatic infection/AIDS. This study examined the associations among fatigue, depressive symptoms, subjective neurocognitive complaints, and objective neuropsychological performance in HIV/AIDS. Sixty-eight men with HIV-infection (27 adults with HIV-infection but not AIDS and 41 with AIDS diagnosis) completed a neuropsychological test battery and self-report measures of fatigue (Fatigue Severity Scale), depressive symptoms (Beck Depression Inventory), and subjective neurocognitive complaints (Patient’s Assessment of Own Functioning). High levels of fatigue were endorsed by participants. Fatigue severity was related to depressive symptoms but not to AIDS diagnosis or medication status. Verbal learning and motor function was worse in participants with AIDS, but neuropsychological functioning was not significantly correlated with fatigue or depressive symptoms. Subjective neurocognitive complaints were predicted by both depressive symptoms and fatigue. Our results suggest that adults with fatigue and HIV-infection (with or without AIDS) should be screened for depression. Neither fatigue nor depressive symptoms appear to affect neuropsychological functioning in HIV/AIDS. Future research is needed to develop and evaluate instruments and methods to differentiate depression-related fatigue from fatigue that may reflect underlying medical disease. Such research will further the development of effective treatments for fatigue associated with HIV-infection.

Fatigue is present in 2–27% of asymptomatic HIV-infected individuals and 30–54% of adults with acquired immune deficiency syndrome (AIDS; Ferrando, Evans et al., 1998). Several studies have demonstrated that fatigue is significantly associated with depression (Ferrando, Evans et al., 1998; Kalichman, Sikkema, & Somlai, 1995; O’Dell, Meighen, & Riggs, 1996; Perkins et al., 1995), disability status, and physical limitations in HIV-infection (Ferrando, Evans et al., 1998). In two recent studies (Ferrando, Evans et al., 1998; Perkins et al., 1995), samples of individuals with asymptomatic HIV-infection (Perkins et al., 1995) and those with good immunological status (i.e., CD4 > 500) (Ferrando, Evans et al., 1998; Perkins et al., 1995) reported levels of fatigue that did not differ significantly from fatigue levels in HIV-negative controls. In the study by Ferrando and colleagues (Ferrando, Evans et al., 1998), changes in scores on the Beck Depression Inventory were associated with significant changes in fatigue level at 1-year follow-up. Similarly, Perkins and associates (Perkins et al., 1995) reported that changes in Hamilton...
Depression Rating Scale scores were significantly predictive of fatigue level at 6-month follow-up. In the latter study (Perkins et al., 1995), fatigue severity was unrelated to neuropsychological functioning at both baseline and follow-up examinations.

Estimates of the prevalence of recent or current major depressive disorder (i.e., in the past 1–2 months) among individuals with HIV or AIDS range from 5 to 23% (Atkinson et al., 1988; Ciesla & Roberts, 2001; Williams, Rabkin, Remien, Gorman, & Ehrhardt, 1991). Neuropsychological impairment has been reported to occur in 44% of mildly symptomatic HIV-infected individuals and 55% of persons with AIDS (Heaton et al., 1995). In contrast to the limited literature on fatigue, the relationship between depression and neuropsychological functioning in HIV and AIDS has received considerable attention. Overall, these studies have concluded that depression appears to be independent of neuropsychological functioning in individuals with HIV or AIDS (Bornstein et al., 1993; Goggin et al., 1997; Grant et al., 1993; Mapou et al., 1993; Richardson et al., 1999). Depressive symptoms are, however, associated with higher rates of subjective neuropsychological complaints (Hinkin et al., 1996; Moore et al., 1997; Rourke, Halman, & Bassel, 1999a; Rourke, Halman, & Bassel, 1999b; van Gorp et al., 1991).

Subjective neuropsychological complaints are often correlated with depression or other psychological symptoms and not with objective measures of neuropsychological performance. This pattern has been found in studies of individuals with multiple sclerosis (MS; Landro, Sletvold, & Celius, 2000; Maor, Olmer, & Mozes, 2001), chronic fatigue syndrome (CFS; Altay et al., 1990), fibromyalgia (Grace, Nielson, Hopkins, & Berg, 1999), Lyme borreliosis (Barr, Rastogi, Ravdin, & Hilton, 1999; Elkins, Pollina, Scheffer, & Krupp, 1999; Ravdin, Hilton, Primeau, Clements, & Barr, 1996), traumatic brain injury (Cicerone & Kalmar, 1995; Lanno et al., 1998), cancer (Cull et al., 1996), and HIV-infection (Maj et al., 1994; Moore et al., 1997; Rourke et al., 1999a; Rourke et al., 1999b; van Gorp et al., 1991; Wilkins et al., 1991), as well as in healthy adults (Chan, 2001; Matotek, Saling, Gates, & Sedal, 2001). In contrast, significant inverse relationships between subjective complaints and neuropsychological test performance have been reported in studies of MS (Matotek et al., 2001), traumatic brain injury (Gass & Apple, 1997), and healthy control participants (Piazza, Canevini, Maggiori, & Canger, 2001). While this relationship is rarely found in other disorders, studies of individuals with HIV/AIDS frequently show an association between subjective neurocognitive complaints and objective functioning (Beason-Hazen, Nasrallah, & Bornstein, 1994; Kim et al., 2001; Poutiainen, 1996; Poutiainen & Elovaara, 1996; Rourke et al., 1999a; Rourke et al., 1999b; Stern et al., 1992). In some cases, this relationship is limited to specific types of complaints (e.g., motor complaints (Lopez, Wess, Sanchez, Dew, & Becker, 1998; Wilkins et al., 1991)) or individuals with symptomatic disease (Poutiainen, 1996). Recent findings suggest that some individuals can accurately assess their cognitive functioning, while others over- or under-estimate their performance (Hinkin et al., 1996; Rourke et al., 1999b). Depression is associated with excessive cognitive complaints, whereas those with more severe objective impairment, particularly on measures reflecting frontal-executive skills (Rourke et al., 1999b), tend to under-report cognitive difficulties.

Previous research on the relationship between fatigue and neuropsychological functioning has shown mixed results. Several studies have found no relationship between fatigue severity and objective neuropsychological test performance in adults with MS (Archibald & Fisk, 2000; Geisler et al., 1996; Johnson, Lange, DeLuca, Korn, & Natelson, 1997; Pollina, Kaufman, Masur, & Krupp, 1998; Schwartz, Coulthard-Morris, & Zeng, 1996) and HIV-infection (Perkins et al., 1995). However, other researchers have reported an association between fatigue severity (or the presence of severe fatigue) and poorer neuropsychological functioning in adults with Lyme borreliosis (Ravdin et al., 1996), post-polio syndrome (Bruno, Galski, & DeLuca, 1993), and CFS (Blackwood, MacHale, Power, Goodwin, & Lawrie, 1998; Ross, Fantie, Straus, & Grafman, 2001). In addition, some studies have found an association between fatigue and structural or functional neuroimaging abnormalities...
in Parkinson’s disease (Abe, Takanashi, & Yanagihara, 2000; Perkins et al., 1995), MS (Colombo et al., 2000; Filippi et al., 2002; Leocani et al., 2001; Moller, Wiedemann, Rohde, Backmund, & Sonntag, 1994; Roelke et al., 1997), and CFS (Fischler et al., 1996), while some have not found brain abnormalities in individuals with MS-related fatigue (Codella, Rocca, Colombo, Martinelli-Boneschi et al., 2002; Codella, Rocca, Colombo, Rossi, 2002; Mainero et al., 1999).

The aim of the present study was to determine the extent to which fatigue and depressive symptoms are associated with subjective neurocognitive complaints and objective neuropsychological functioning in individuals with HIV and AIDS. Since rates of neuropsychological impairment (Heaton et al., 1995), fatigue (Darko, McCutchan, Kripke, Gillin, & Golshan, 1992) and subjective neurocognitive complaints (Mehta et al., 1996) have been shown to increase with HIV disease progression, we wished to determine whether fatigue would be related to increased neurocognitive complaints and poorer neuropsychological performance in these participants. Our primary hypotheses were: (1) levels of fatigue, depressive symptoms, subjective neurocognitive complaints, and neuropsychological impairment would be higher among participants with AIDS than in individuals with primarily symptomatic HIV-infection who did not meet criteria for AIDS; (2) fatigue and depressive symptoms would be significantly associated with each other and with subjective neurocognitive complaints; and (3) objective neuropsychological functioning would be significantly correlated with subjective neurocognitive complaints but not with fatigue or depressive symptoms.

METHOD

Participants

Participants in this study were 68 adult men with HIV-infection who underwent a comprehensive neuropsychological assessment in the context of an ongoing observational study of the neurobehavioral complications in HIV/AIDS. The study is approved by the St. Michael’s Hospital Research Ethics Board and all participants provided written informed consent. The participant sample was predominantly Caucasian and the majority of this sample reported homosexual contact as a major risk factor for HIV-infection. The questionnaires and neuropsychological tests were administered to participants in one or two sessions, requiring a total of 3–4 hr. The vast majority of participants (i.e., 90%) completed all tests and questionnaires in 1 day. The remaining 7 participants completed testing in two sessions approximately 1–2 weeks apart. The fatigue scale was completed on the same day as some or all of the neuropsychological tests. Only participants who completed the Fatigue Assessment Instrument (Schwartz, Jandorf, & Krupp, 1993) were included in the present analysis. Fatigue scores were available for 71 participants, but box plots and multivariate tests revealed one outlier on measures of fatigue severity as a function of AIDS and depression status. Data for this individual were removed, as were data for 2 participants whose test sessions occurred more than 3 weeks apart. This resulted in a final sample size of 68 cases. These participants were tested between December 1997 and May 1999. Of the 68 participants, 5 were asymptomatic (CDC93 A1 and A2), 22 were mildly symptomatic (CDC93 B1 and B2), and 41 had AIDS-defining illnesses or a current or past CD4 lymphocyte count less than 200 (CDC93 A3 [n = 1], B3 [n = 21] and C1–C3 [n = 19]); Centers for Disease Control and Prevention (CDC), 1992). Data from the asymptomatic and mildly symptomatic subjects were combined to form the HIV-infection without AIDS group (non-AIDS, n = 27). Demographic data for the two groups are shown in Table 1. The non-AIDS and AIDS groups did not differ with respect to age or education. As expected, the AIDS group had a lower recent CD4 count than the non-AIDS group. Fifteen of 27 participants (56%) in the non-AIDS group were taking highly active antiretroviral therapy (HAART) medication, compared to 28 of 41 (68%) in the AIDS group (p = .23). There were no differences in the percentage of participants taking antidepressants (33% of non-AIDS, 39% of AIDS; p = .63) or benzodiazepines (22% of non-AIDS, 27% of AIDS; p = .67). Participants were excluded with a history of CNS opportunistic infection and inflammatory conditions with prominent fatigue symptomatology (e.g., MS, lupus, and fibromyalgia).

Measures

Fatigue

The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) is a 9-item scale that measures the subjective experience of fatigue and the extent of its impact on everyday functioning. Each item presents the participant with a statement (e.g., “My
motivation is lower when I am fatigued,” “I am easily fatigued,” “Fatigue interferes with my work, family, or social life”). For each statement, the participant is asked to indicate the extent to which he/she agrees with the statement using a Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree). Participants are asked to respond to items as they apply to the previous 2 weeks. Higher scores represent higher levels of fatigue. The FSS score is the average of the 9 items. The FSS has been used in studies of fatigue in multiple sclerosis (Krupp & Elkins, 2000; Krupp et al., 1989; Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994), systemic lupus erythematosus (Krupp et al., 1989), chronic fatigue syndrome (Krupp et al., 1994), eosinophilia-myalgia syndrome (Pollina, Kaufman, Masur, & Krupp, 1998), and chronic hepatitis C (Kleinman et al., 2000). The reliability of the FSS has been well documented (Kleinman et al., 2000; Krupp et al., 1989). It has also been shown to have construct validity (i.e., it correlates highly with other measures of fatigue) and is sensitive to changes in fatigue level (e.g., as a result of treatment) (Krupp et al., 1989; Rammohan et al., 2002). To our knowledge, the FSS has not been used previously to assess fatigue in individuals with HIV-infection or AIDS.

In the present study, participants completed the 29-item Fatigue Assessment Instrument (FAI; Schwartz et al., 1993). The FAI includes the 9-item FSS. In order to facilitate comparison with studies using the FSS in other populations, only data from the FSS are reported here. The FSS score is the average of responses to the 9-item FSS.

Depression
Depressive symptoms were measured using the Beck Depression Inventory (BDI; Beck & Steer, 1993). The BDI is a 21-item instrument, with the first 13 items (BDI-Cog) reflecting cognitive-affective symptoms (e.g., sadness, guilt) and the remaining 8 items (BDI-Som) reflecting somatic or vegetative symptoms (e.g., sleep or appetite disturbance; Beck & Steer, 1993). Scores of 11 or above on the cognitive-affective scale (BDI-Cog), or 16 or above on the total score (BDI-Tot), are suggestive of clinical depression (Beck & Steer, 1993). Since the BDI contains one item relating to fatigue (Item 17), this item was removed from the BDI.

### Table 1. Comparison of AIDS and Non-AIDS Groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-infection without AIDS (Non-AIDS)</th>
<th>AIDS (n = 27)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39.9 (8.9)</td>
<td>40.3 (7.9)</td>
<td>.85</td>
</tr>
<tr>
<td>Education</td>
<td>13.6 (3.2)</td>
<td>14.0 (2.8)</td>
<td>.53</td>
</tr>
<tr>
<td>Most recent CD4 count</td>
<td>484.4 (220.4)</td>
<td>281.6 (204.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Viral load &lt;500 copies</td>
<td>67%</td>
<td>59%</td>
<td>.53</td>
</tr>
<tr>
<td>Percent on established HAART regimen</td>
<td>56%</td>
<td>70%</td>
<td>.23</td>
</tr>
<tr>
<td>Percent on antidepressant medication</td>
<td>33%</td>
<td>39%</td>
<td>.63</td>
</tr>
</tbody>
</table>

**Behavioral measures:**
- Fatigue Severity Scale score: 5.3 (1.3) vs. 5.5 (1.2), p = .47
- Total BDI score: 15.4 (10.2) vs. 17.7 (9.4), p = .34
- BDI Cognitive-Affective score: 10.2 (7.3) vs. 10.9 (6.7), p = .69
- BDI Somatic score: 5.2 (3.5) vs. 6.8 (3.9), p = .09
- Total neurocognitive complaints (PAOF): 54.1 (26.9) vs. 60.2 (26.2), p = .36

**Neuropsychological tests (raw scores):**
- CVLT Total Words (Trials 1–5): 50.6 (10.0) vs. 45.1 (11.3), p = .04
- Digit Symbol: 52.3 (11.0) vs. 50.4 (13.6), p = .55
- Symbol Digit Modalities Test: 50.6 (9.5) vs. 46.4 (10.6), p = .10
- Trail Making Test – Part A (s): 28.1 (10.1) vs. 30.4 (13.3), p = .45
- Trail Making Test – Part B (s): 66.4 (31.8) vs. 75.9 (36.9), p = .28
- Grooved Pegboard Dominant Hand (s): 68.6 (10.1) vs. 77.8 (19.5), p = .01
- Grooved Pegboard Nondominant Hand (s): 72.9 (10.5) vs. 80.1 (16.7), p = .03

1Item 17 (fatigability) was not included in this total.
2n = 26.
total score (BDI-Tot) and somatic symptoms score (BDI-Som) prior to conducting the correlational analyses (Hypotheses 2 and 3).

**Neurocognitive Complaints**
Subjective neurocognitive complaints were assessed using the Patient’s Assessment of Own Functioning Inventory (PAOF; Chelune, Heaton, & Lehman, 1986). The PAOF is a self-report questionnaire that asks participants to rate how often they experience specific difficulties with memory, language and communication, sensory-perceptual and motor skills, and higher-level (executive) cognitive functions. Previous studies in our laboratory have shown that the PAOF scores of participants with HIV-infection are associated with both depression and objective neuropsychological test performance (Rourke et al., 1999a; Rourke et al., 1999b). In the present study, the PAOF total score (PAOF-Tot) was used as an index of overall severity of subjective neurocognitive complaints.

**Neuropsychological Performance**
Neuropsychological tests were selected according to guidelines developed by the National Institute of Mental Health Workshop on Neuropsychological Assessment Approaches for AIDS-related Cognitive Changes (Butters et al., 1990). Test scores analyzed in the present study were selected from the larger set in the ongoing study (Rourke et al., 1999a) and the restricted set of tests included measures of verbal learning, psychomotor speed, and motor speed/dexterity: California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987), WAIS-R Digit Symbol (Wechsler, 1981), Symbol Digit Modalities Test (Smith, 1973), Trail Making Test: Parts A and B (Reitan & Wolfson, 1993), and Grooved Pegboard Test (Heaton, Grant, & Matthews, 1991). A subset of measures from the larger battery was chosen in order to reduce the number of comparisons. Specific tests were chosen to represent those ability areas most affected in HIV-infection and those potentially affected by fatigue.

The distributions of the neuropsychological test performance variables were examined for the presence of outliers (scores more than 329 SDs away from the mean). The following test variables had outliers: Grooved Pegboard Dominant Hand \((n = 2)\), Grooved Pegboard Nondominant Hand \((n = 2)\), Trails A \((n = 1)\), and Trails B \((n = 1)\). All the participants with scores identified as outliers were in the AIDS group. Extreme scores were assigned values that were one unit larger than the next most extreme score (Tabachnick & Fidell, 1996).

**Statistical Analyses**
To test our three hypotheses, we conducted the following statistical analyses. For Hypothesis 1, \( t \) tests were used to compare the two groups (HIV-infected without AIDS and with AIDS diagnosis) with respect to fatigue, depressive symptoms, subjective neurocognitive complaints, and objective neuropsychological performance (raw test scores). An alpha level of .05 was adopted for these analyses.

For Hypothesis 2, a series of analyses were performed to examine the association between fatigue and depression. Correlational analyses were used to examine the relationship between BDI scores (BDI-Cog and BDI-Som) and Fatigue Severity (FSS) scores. Analysis of variance (ANOVA) was conducted to assess the effects of HIV disease severity (AIDS vs. non-AIDS) and depression status (depressed or not) on fatigue severity (FSS). For the purposes of the latter analysis, participants were categorized as depressed (i.e., DEP+) if their BDI-Cog was >10 or not depressed (i.e., DEP−) if BDI-Cog ≤10. The effect of depression severity on fatigue level was examined using a Kruskal–Wallis test with post hoc Mann–Whitney \( U \) tests. For these analyses, participants were classified according to the following levels of depression severity (based on BDI total score; Beck & Steer, 1993): minimal (BDI < 10), mild (BDI = 10–16), moderate (BDI = 17–29), and severe (BDI = 30+). A series of analyses were conducted to examine the relationship between fatigue, depressive symptoms, and subjective neurocognitive complaints. Spearman correlations between BDI scores (BDI-Cog and BDI-Som), Fatigue Severity (FSS) scores, and subjective neurocognitive complaints (PAOF-Tot) were calculated. Next, stepwise multiple regression analysis was used to explore the relationships among fatigue, cognitive-affective depressive symptoms (BDI-Cog), and subjective neurocognitive complaints (PAOF-Tot). In the multiple regression analysis, total neurocognitive complaints (PAOF-Tot) was the dependent variable and FSS score (Step 1) and BDI-Cog (Step 2) were entered as predictors.

To address Hypothesis 3, Spearman correlation analyses were used to examine the associations between fatigue, depressive symptoms, subjective neurocognitive complaints, and objective neuropsychological test performance. All analyses were carried out using SPSS 10.0 for Windows. An alpha level of .01 was adopted as the criterion for statistical significance for all correlational analyses.

**RESULTS**

**Comparison of AIDS Versus Non-AIDS Groups**
Overall, the AIDS and non-AIDS groups did not differ with respect to severity of fatigue,
depressive symptoms, or subjective neuropsychological complaints. The AIDS group demonstrated poorer performance on verbal learning (CVLT Total 1–5; t(66) = 2.06, p < .05) and motor speed/dexterity (Grooved Pegboard Dominant and Nondominant hand trials (t(66) = −2.55, p < .05; t(66) = 2.17, p < .05, respectively). The performance of the AIDS and non-AIDS groups did not differ on other tests of psychomotor speed (Digit Symbol, Symbol Digit Modalities Test, Trail Making Test; all ps > .05).

**Table 2. Spearman Correlations Between Fatigue, Depressive Symptoms, Neurocognitive Complaints, and Neuropsychological Performance.**

<table>
<thead>
<tr>
<th>Test score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSS</td>
<td>−.38</td>
<td>.60</td>
<td>.48</td>
<td>.01</td>
<td>−.26</td>
<td>−.24</td>
<td>−.01</td>
<td>.15</td>
<td>.12</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>BDI-Cog</td>
<td>−.62</td>
<td>.54</td>
<td>−.05</td>
<td>−.15</td>
<td>−.03</td>
<td>−.10</td>
<td>.15</td>
<td>.01</td>
<td>−.02</td>
<td></td>
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<tr>
<td>BDI-Som1</td>
<td>−.52</td>
<td>−.23</td>
<td>−.23</td>
<td>−.24</td>
<td>.09</td>
<td>.18</td>
<td>.04</td>
<td>.08</td>
<td></td>
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<tr>
<td>PAOF-Tot</td>
<td></td>
<td>−.30</td>
<td>−.54</td>
<td>−.39</td>
<td>.23</td>
<td>.48</td>
<td>.33</td>
<td>.39</td>
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<tr>
<td>CVLT</td>
<td></td>
<td></td>
<td>.48</td>
<td>.55</td>
<td>−.32</td>
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<td>−.52</td>
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<tr>
<td>Digit Symbol</td>
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<td></td>
<td></td>
<td>.82</td>
<td>−.57</td>
<td>−.72</td>
<td>−.65</td>
<td>−.76</td>
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<tr>
<td>SDMT</td>
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<td></td>
<td></td>
<td>−.66</td>
<td>−.70</td>
<td>−.66</td>
<td>−.72</td>
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</tr>
<tr>
<td>Trails A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.64</td>
<td>.34</td>
<td>.46</td>
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<td>Trails B</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>.45</td>
<td>.59</td>
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<td>Pegs DH</td>
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</table>

*Note. FSS = Fatigue Severity Scale, BDI-Cog = Cognitive-Affective symptoms, BDI-Som = Somatic symptoms, PAOF-Tot = Total neurocognitive complaints, CVLT = Verbal learning total trials 1–5, SDMT = Symbol Digit Modalities Test, Pegs DH = Grooved Pegboard Dominant Hand, Pegs NH = Grooved Pegboard Nondominant Hand.

1Item 17 (fatigability) was not included in this total.

* p < .05. ** p < .01.

**Relationship Between Fatigue and Depression**

As predicted, all analyses indicated a strong association between depressive symptoms and fatigue severity. Because the distribution of FSS scores was negatively skewed (skewness = −3.63, kurtosis = 0.78), Spearman correlations were used to examine the relationship between BDI scores and Fatigue Severity scores. These analyses indicated that fatigue severity (FSS) and depressive symptoms (BDI-Cog and BDI-Som) were highly correlated (p < .01, see Table 2).

A 2 × 2 analysis of variance (ANOVA) was conducted to assess the effect of HIV disease severity (AIDS vs. non-AIDS) and depression status (DEP+ vs. DEP−) on fatigue severity (FSS). This analysis revealed a main effect of depression (F(1, 64) = 8.37, p < .01), with depressed participants demonstrating higher FSS scores. Neither AIDS status, nor the interaction of AIDS status and depression, had a significant effect on fatigue severity (p > .05).1 Figure 1 shows fatigue severity as a function of AIDS and depression status.

When all participants were classified into four levels of depression severity, the following groups were formed: minimal (n = 14), mild (n = 18), moderate (n = 27), and severe (n = 9). The frequency of these depression severity classifications did not differ as a function of AIDS status (χ²(3, N = 68) = 3.64, p = .30). A Kruskal–Wallis test indicated that FSS scores differed significantly across the four depression severity groups (χ²(3, N = 68) = 19.28, p < .001). Post hoc Mann–Whitney tests showed that FSS scores were significantly higher in the moderate and severe groups, compared to the minimal group.

1While the FSS scores of the four AIDS × DEP groups did not show homogeneity of variance (Levene’s F(3, 64) = 6.54, p = .001), this was not felt to be a significant problem given that ANOVA is considered to be robust when the ratio of the largest group size to the smallest is four or less (1.9 in this analysis) and the ratio of the largest group variance to the smallest (Fmax) is 10 or less (5.3 for the AIDS × DEP groups). Tabachnick and Fidell (1996). Using multivariate statistics. New York, NY: Harper & Row Publishers.
(p < .01), and in the severe group compared to the mild and moderate groups (p < .05). The relationship between depression severity and fatigue is shown in Figure 2.

**Relationship Between Fatigue, Depressive Symptoms, and Neurocognitive Complaints**

Measures of fatigue (FSS), depressive symptoms (BDI-Cog, BDI-Som), and subjective neurocognitive complaints (PAOF-Tot) were all highly correlated (p < .01, see Table 2). Stepwise multiple regression revealed that fatigue severity and depressive symptoms (BDI-Cog) were independent predictors of subjective neurocognitive complaints ($R^2$ change = .25 (p < .001) for fatigue and .12 (p < .01) for depressive symptoms).

**Relationship Between Fatigue, Depressive Symptoms, Subjective Neurocognitive Complaints, and Neuropsychological Functioning**

Neither fatigue nor depressive symptoms correlated significantly with any neuropsychological test measure (all ps ns). Subjective neurocognitive
complaints (PAOF-Tot) were significantly correlated \((p < .01)\) with performance on Digit Symbol, Symbol Digit Modalities Test, Trails B, and Grooved Pegboard Dominant and Nondominant Hand Trials.

**Relationship Between Fatigue and Medication Status**

Although it was not a focus of the study, we wished to ensure that fatigue levels were not influenced by medication effects; since antiretroviral (ARV) medications are known to cause fatigue (Barroso, 1999; Duran et al., 2001; Zinkernagel et al., 1999). In order to evaluate the contribution of medication as a potential confound, participants were classified according to whether they were taking an established or investigational HAART regimen \((n = 45)\), suboptimal therapy (e.g., AZT and 3TC only; \(n = 12)\), or no antiretroviral medication \((n = 10)\). Information for 1 participant was missing. A one-way analysis of variance (ANOVA) revealed no significant differences in fatigue severity between the three ARV groups \((F(2, 64) = 0.32, p = .73)\). Similarly, fatigue levels did not differ with use of antidepressants \((t(66) = -1.66, p = .10)\) or benzodiazepines \((t(66) = -0.66, p = .51)\).

**DISCUSSION**

In the present study, higher levels of fatigue in HIV/AIDS were significantly associated with the presence of depression (defined using the BDI) and with increasing severity of depressive symptoms. These results are consistent with studies in asymptomatic HIV-infection (Perkins et al., 1995), multiple sclerosis (Schwartz et al., 1996), and systemic lupus erythematosus (SLE; Krupp, LaRocca, Muir, & Sternberg, 1990) that have reported an association between fatigue and depression. Fatigue level was independent of neuropsychological functioning in our sample of adults with HIV-infection. The relationship between fatigue and neuropsychological functioning has been studied in other clinical conditions, such as multiple sclerosis and chronic fatigue syndrome, in which fatigue is a prominent complaint. The majority of these studies report no association between fatigue and performance on neuropsychological tests (Archibald & Fisk, 2000; Geisler et al., 1996; Johnson et al., 1997; Pollina et al., 1998; Schwartz et al., 1996). However, associations between fatigue and performance on tests of attention and memory have been reported (Blackwood et al., 1998; Bruno et al., 1993; Ravdin et al., 1996; Ross et al., 2001). It is possible that significant relationships between HIV-related fatigue and neuropsychological functioning might be demonstrated using more demanding attention tasks or by using measures of fatigue that are less affected by mood.

Participants with AIDS performed worse than those without AIDS diagnosis on measures of verbal learning and motor speed/dexterity. These findings suggest greater severity of CNS dysfunction, and specifically subcortical dysfunction, in adults with AIDS. These findings are consistent with previous reports of a subcortical pattern of impairment in HIV/AIDS.

Fatigue and apathy are often reported by individuals with subcortical disorders (King & Caine, 1990). Functional brain imaging techniques have demonstrated an association between fatigue and frontal/subcortical dysfunction in adults with Parkinson’s disease (Abe et al., 2000; Ross et al., 2001), MS (Filippi et al., 2002; Roelcke et al., 1997), and chronic fatigue syndrome (CFS; Fischler et al., 1996). It has been suggested that fatigue in HIV-infection may be related to subcortical CNS dysfunction (Perkins et al., 1995). However, the absence of an association between fatigue and neuropsychological functioning in the present study implies that fatigue (at least as measured by the Fatigue Severity Scale) is not a useful marker of subcortical functioning. Further research is needed to examine the relationship between fatigue and other subcortical symptoms, such as apathy. Castellon et al. (Castellon, Hinkin, Wood, & Yarema, 1998) studied the relationships between apathy (a condition that may be similar to fatigue), depression, and neuropsychological functioning in HIV. They reported that apathy, but not depression, was associated with poorer working memory performance. Conversely, Rabkin et al. (2000) found that apathy was related to...
depression but not to neuropsychological functioning. These discrepant findings may relate to differences in neuropsychological tests and apathy measures.

Overall, participants with HIV-infection in our study (with and without AIDS diagnosis) reported high levels of fatigue. The average fatigue severity scale score in our sample was 5.4 ($SD = 1.3$). This score is higher than mean scores reported for samples of adults with multiple sclerosis (4.8; Krupp et al., 1989, 5.2; Packer, Sauriol, & Brouwer, 1994), systemic lupus erythematosus (4.7; Krupp et al., 1989, 4.6; Krupp et al., 1990), sleep disorders (4.8; Lichstein, Means, Noe, & Aguillard, 1997), post-polio syndrome (4.8; Packer, Martins, Krefting, & Brouwer, 1991, 5.1; Packer et al., 1994), eosinophilia-myalgia syndrome (5.0; Pollina et al., 1998), or chronic hepatitis C (3.8; Kleinman et al., 2000), but lower than mean scores for other samples with chronic fatigue syndrome (5.7; Krupp et al., 1994, 6.1; Packer et al., 1994) multiple sclerosis (5.6; Krupp et al., 1994), and immune-mediated polyneuropathies (5.6; Merkies, Schmitz, Samijn, van der Meche, & van Doorn, 1999). Fifty-nine of 68 participants (87%) obtained scores of 4 or above (the cutoff for significant fatigue recommended by Krupp & Elkins, 2000). Fatigue in individuals with HIV-infection may have many causes. These include opportunistic infections, medications, wasting, and depression, among others (Walker, McGown, Jantos, & Anson, 1997). Fatigue in any one individual may be related to one or many factors that may or may not be directly related to having HIV/AIDS. Longitudinal studies are necessary to examine how different factors directly and indirectly contribute to fatigue over time.

The fact that FSS scores were negatively skewed in this sample suggests that the FSS may not be sensitive to variations in fatigue levels within the HIV/AIDS population. Similarly, the Fatigue Severity Scale used in the present study does not distinguish between physical and mental fatigue symptoms (Paul, Beatty, Schneider, Blanco, & Hames, 1998). Fatigue associated with AIDS may be qualitatively different from fatigue in HIV-infected individuals without AIDS. In contrast to our prediction, participants with HIV-infection and AIDS did not show higher levels of fatigue compared to non-AIDS subjects. Asymptomatic HIV-infected subjects were under-represented in the present study. Further research is needed to examine fatigue in samples representing a broader range of HIV-illness severity.

Fatigue is a difficult construct to define and measure. More research is needed to investigate relationships among different fatigue scales, as well as the overlap between measures of fatigue, depression, and apathy. The Fatigue Severity Scale (Krupp et al., 1989), used in the present study, was originally developed for studies of multiple sclerosis and lupus. The FSS was chosen for use in this study because it has been shown to have good psychometric properties (e.g., reliability, validity, sensitivity to change in fatigue level with treatment) (Merkies et al., 1999; Kleinman et al., 2000; Krupp et al., 1989; Rammohan et al., 2002) and it has been used in studies with a variety of clinical populations. Some FSS items appear to assess the subjective impact of fatigue (e.g., “Fatigue interferes with my physical functioning”), while others relate more directly to fatigue severity (e.g., “Fatigue is among my three most disabling symptoms”). Despite this apparent heterogeneity, the results of a recent study using item response theory suggest that the FSS measures only a single domain (Kleinman et al., 2000). Further research is needed to evaluate the relationship between cognitive functioning and fatigue level during testing versus typical fatigue level. For example, Bruno et al. (1993) found that participants with post-polio syndrome who typically experienced severe fatigue performed more poorly on tests of attention and concentration even when their self-reported fatigue levels at the time of testing were relatively low. Chronic fatigue may be more closely associated with underlying central nervous system dysfunction than acute fatigue, which may be more related to sleep disturbance or medication effects.

The Piper Fatigue Scale (PFS; Piper et al., 1998; Piper et al., 1989), originally developed for use with cancer patients, may provide a broader measure of fatigue for use in studies of HIV-infection. A 22-item version of the PFS (Piper
et al., 1998) contains four subscales: behavioral/severity, affect meaning, sensory, and cognitive/mood. Breitbart and colleagues (Breitbart, Rosenfeld, Kaim, & Funesti-Esch, 2001) used three measures of fatigue (the PFS (Piper et al., 1989), a visual analogue scale (Lee, Hicks, & Nin-Murcia, 1991), and an objective measure of muscular endurance (Lenman, Tulley, Vrbova, Dimitrijevic, & Towle, 1989)). They found significant decreases in PFS scores among HIV-infected individuals receiving psychostimulants (methylphenidate or pemoline) compared to a placebo control group. Grady and coworkers (Grady, Anderson, & Chase, 1998) also demonstrated the sensitivity of a modified PFS to changes in fatigue in HIV-illness. In their study, treatment with interleukin-2 was associated with increased fatigue.

Although there is no consensus on the relationship between viral load and fatigue (Barroso, 1999), previous studies have generally found a relationship between markers of immune status (e.g., CD4 counts) and measures of fatigue (Darko et al., 1992; Walker et al., 1997). In the present study, participants with an undetectable viral load (<500 copies/ml) did not differ with respect to fatigue severity from those with a detectable viral load (t(64) = −0.06, p = .96). In addition, fatigue scores were not significantly associated with the logarithm of viral load (Spearman r = .18, p = .15). However, participants with lower CD4 counts reported higher levels of fatigue (Spearman r = −0.29, p < .05). Because of this result, we re-ran our ANOVA analyses using CD4 count as a covariate and the results were essentially unchanged.

Fatigue scores did not distinguish participants on HAART (the majority of the present sample) from those on suboptimal ARV therapy or no ARV medication. Most previous studies of fatigue in HIV-infection were conducted prior to the introduction of HAART. Recent research suggests that HAART may improve cognitive functioning (Ferrando, van Gorp et al., 1998b; Sacktor et al., 1998; Sacktor et al., 1999; Sacktor et al., 2000; Tozzi et al., 2001). However, ARV medication may also cause fatigue (Barroso, 1999; Duran et al., 2001; Zinkernagel et al., 1999). Further research is needed to examine the relationship between ARV medications and fatigue in HIV/AIDS.

The present study is limited by a relatively small sample size. Given the exploratory nature of the study, we adopted an alpha level of .01 for the correlational analyses used to evaluate our primary hypotheses and an alpha level of .05 for other analyses. Nonetheless, carrying out multiple analyses on a sample of this size increases the risk that some apparently significant results may have occurred by chance. Future research should examine the relationship between fatigue and neuropsychological functioning in larger samples of individuals with HIV-infection. Including a larger group of individuals who are asymptomatic may provide a less skewed distribution of fatigue scores. A significant proportion of the participants in the present study showed normal performance on neuropsychological testing. Different relationships between fatigue and neuropsychological performance might be found among adults with minor cognitive motor disorder (MCMD) or HIV-associated dementia complex. The cross-sectional nature of the present study also limits the generalizability and clinical implications of our findings. Prospective studies are needed to explore the temporal relationships between fatigue, neuropsychological impairment, and other symptoms of HIV-infection, especially with disease progression and treatment with HAART. Future studies are underway in our laboratory to address these limitations.

In summary, the principal finding of this study was that fatigue and depressive symptoms are significantly related to each other and to subjective neurocognitive complaints, but not to objective neuropsychological performance, in individuals with HIV/AIDS. These results suggest that severe fatigue does not confound accurate assessment of neuropsychological functioning in this population. These findings also underscore the importance of screening for depression. Successful treatment for depressive symptoms (e.g., with antidepressant medication (Elliott et al., 1998) and/or psychotherapy (Levine, Bystritsky, Baron, & Jones, 1991) may significantly improve quality of life by reducing fatigue and subjective neurocognitive complaints. Interventions to treat fatigue directly for example, medication
(Breitbart et al., 2001) or exercise (Smith et al., 2001) may have similarly beneficial effects and require clinical trials to evaluate their potential efficacy.

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