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Treatment of HIV-Related Fatigue with Armodafinil: A Placebo-controlled Randomized Trial

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Abstract

Objective—To evaluate the efficacy and safety of armodafinil in the treatment of fatigue in HIV + patients, and to assess effect on depressive symptoms and behavior once fatigue remitted.

Method—HIV+ patients with clinically significant fatigue were treated in a placebo controlled randomized double-blind trial for 4 weeks. Armodafinil responders and placebo non-responders or relapsers were treated openly for a total of 16 weeks of armodafinil. The primary outcome measure for fatigue and depression was the Clinical Global Impressions-Improvement Scale, supplemented by the Fatigue Severity Scale, Hamilton Depression Rating Scale and Beck Depression Inventory. Safety was assessed with assays of CD4 cell count and HIV RNA viral load and the SAFTEE side effects rating scale. Maximum trial dose of armodafinil was 250 mg/day.

Results—70 patients were enrolled. Attrition was 9%. In Intention-to-treat analyses, fatigue response rate to armodafinil was 75% and to placebo, 26%. Armodafinil did not reduce depressive symptoms in the absence of improved energy, but of those patients with an Axis I depressive disorder at study entry whose energy improved, 82% experienced improved mood as well. Markers of immunologic suppression did not change during treatment. At 6 months, those still taking armodafinil had more energy and fewer depressive symptoms than those who were no longer taking it.

Conclusions—As we found in our RCT of modafinil, armodafinil appears effective and well tolerated in treating fatigue in HIV+ patients. Side effects were minimal and most patients reported substantially improved energy and mood.

INTRODUCTION

Fatigue is common in the context of HIV/AIDS. Investigators have reported prevalence estimates ranging from 30–65%, [1–3] depending on the query, time frame and sample. In

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DISCLOSURE
This study was largely supported by NIMH Grant # R01 MH072383, when the first 48 patients were enrolled. During the final 8 months, partial funding was also received from Cephalon, Inc., as a result of an investigator-initiated request to complete the RCT. Because armodafinil was approved by the FDA but not yet marketed when this RCT was initiated, product and matching placebo were provided by Cephalon throughout the trial. Cephalon Inc. played no role in the design, analysis or reporting of our findings. None of the authors was employed by Cephalon, served as consultants or speakers, or owned stock in the company. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

clinical practice, providers do not routinely inquire about, nor do patients often volunteer information about fatigue and when they do, fatigue is often attributed to depression. However, even in the absence of depression, fatigue can disrupt activities of daily living, as well as more complex activities such as school and employment.[4]

In the context of HIV, fatigue may have multiple and overlapping etiologies, including co-morbid medical conditions such as hepatitis C, anemia, hypogonadism and hypothyroidism. Fatigue may also be secondary to medication side effects. Most investigators have failed to find an association between degree of immunosuppression and fatigue,[2] or demographic variables such as age and ethnicity/race.[1]

There is a circular relationship between fatigue and depression, in that fatigue is one criterion for diagnosis of major depressive disorder,[5] as is impaired concentration, another manifestation of fatigue. Further, since fatigue is associated with restricted activity levels, it has substantial behavioral impact, contributing to social isolation and reduced opportunities for pleasant events, which in turn can lead to depressed mood. Thus, while fatigue and depression are associated,[6,7] both are common among people with HIV/AIDS,[8] and may be present independently.

Modafinil and armodafinil (the r isomer of modafinil) are Schedule IV agents, approved for treatment of the excessive sleepiness associated with narcolepsy and shift work disorder, and as adjunctive treatment in obstructive sleep apnea. As psychostimulants, they have less potential for abuse and are associated with fewer peripheral and central adverse events compared to amphetamines.[9] Pharmacokinetic studies have shown that the elimination half-life of armodafinil is three times greater than that of S modafinil, and that systemic exposure following longterm administration is also approximately three times longer.[10] As noted by Winder-Rhodes et al,[11] "a well-defined biological model of action for modafinil [and by extension, armodafinil] remains to be eluicidated." Ballon and Feifel[12] describe the mechanisms as "complex and distinct from other known wakefulness agents. Modulation of glutamate, GABA, histamine and hypocretin are involved whereas effects on monoamine systems are less important. Anatomically, modafinil's effects focus on the hypothalamus-based wakefulness circuits rather than diffuse neuronal activation (p. 555). " Recent animal studies suggest that the mechanism of action of modafinil on behavior is via dopamine transporter inhibition.[13]

Modafinil has been effective in treating fatigue in other conditions including cancer,[14] multiple sclerosis [15] and amyotrophic lateral sclerosis.[16] Results of both modafinil and armodafinil have been mixed regarding effect on depressive symptoms.[17,18] In a RCT of armodafinil for excessive sleepiness in patients with treated obstructive sleep apnea and co-morbid depression,[19] depressive symptoms improved at least minimally (CGI<4) in the armodafinil group compared to placebo, but no difference was observed on an objective measure of sleepiness. In a proof-of-concept placebo controlled study of 257 depressed patients with bipolar I disorder, those randomized to armodafinil showed greater improvement in depressive symptoms on some but not all measures.[20]

Because the package insert of armodafinil indicates a potential "mild inducer effect" and because armodafinil shares the same CYP metabolic pathway as some antiretroviral medications, we were concerned about possible drug interactions and safety. We thus monitored CD4 and HIV RNA viral load levels at baseline and throughout the study, including a six-month follow-up for patients who completed the trial.

In our previous trial of modafinil for the treatment of clinically significant fatigue in patients with HIV/AIDS, we found a decisive advantage of modafinil over placebo with response rates of 73% and 28%, respectively.[21] The current study is intended to replicate and extend

these findings. Using the same inclusion/exclusion criteria and measures, we conducted a randomized double blind placebo controlled trial of armodafinil in HIV+ patients to assess efficacy in treating fatigue, mood effects, and safety. Study questions were 1) is armodafinil superior to placebo in ameliorating symptoms of fatigue? 2) is armodafinil superior to placebo in reducing depressive symptoms when present at study entry? and 3) Do measures of CD4 cell count and HIV RNA viral load differentially change for patients receiving armodafinil vs. placebo?

METHOD

Sample

Eligible patients were HIV+, ages 21–70, had clinically significant fatigue defined as interference with at least two daily activities on a Role Function Scale, and a score of 41+ on the Fatigue Severity Scale (described below). Patients with untreated major depression, unstable medical condition, untreated conditions associated with fatigue such as anemia, change in antiretroviral medications in the past month or initiation of antidepressant medications in the past 2 months were excluded. We included those with a history of substance use disorders only if they were in partial or full remission for at least 4 months. A complete list of inclusion and exclusion criteria is shown in Table 1.

Study Design—This was a 4-week randomized double-blind placebo-controlled study. At study entry and Week 4, a 1-hour battery of neuropsychological (NP) tests was administered. Week 4 NP change data will be reported elsewhere. Week 4 responders to armodafinil were offered 12 additional weeks of open label medication, and placebo non-responders or relapsers were offered open label armodafinil for 16 weeks. Armodafinil non-responders had their study medication stopped and returned one week later to consider alternative treatments as clinically indicated. Placebo responders were followed without treatment. At the final study visit, patients were given prescriptions for armodafinil; assistance was provided when insurance companies required prior authorization or appeals. Patients were seen for a follow-up visit at six months after initiation of armodafinil, when energy, mood, activity level and CD4 cell count and viral load were again assessed.

Patients were randomized in blocks of four according to a computer-generated list provided by the New York State Psychiatric Institute Research Pharmacy, which also packaged active and placebo armodafinil which were identical in appearance. Medication was dispensed by the study psychiatrist (RR) at each visit. Starting dose was 50 mg/day, increased weekly in the absence of clinical response and dose-limiting side effects to a maximum of 250 mg/day during the last two days of Week 4.

At the initial evaluation, background information, medical and psychiatric history and current medications were elicited, and patients were asked what activities they would engage in if their energy was restored. Bloodwork (described below) was performed, and a letter was faxed to their HIV care provider describing the study and requesting a signed statement that there were no medical contraindications (e.g. cardiac history) to the patient's participation. Eligible patients were then seen by the study psychiatrist at baseline and weekly thereafter during the double blind trial.

The protocol was approved by the New York State Psychiatric Institute Institutional Review Board, and all participants gave written informed consent after being informed of the procedures, risks, and alternatives to study participation. Patients were enrolled between June 2008 and April 2010, with final 6-month visits completed in September 2010.

Measures—The Structured Clinical Interview for DSM-IV (SCID)[22] modules for depression were used to exclude Major Depressive Disorder (MDD), and to identify current MDD in Partial Remission, minor depression and dysthymia, which were permitted. SCID screens were used to identify (and exclude) patients with past or current psychotic conditions and bipolar disorder.

Fatigue

The primary endpoint defining responder vs. non-responder was the Clinical Global Impressions-Improvement Scale (CGI).[23] Scores range from 1 = very much improved to 7 = very much worse. Responders were rated “1” or “2” on energy response compared to baseline; non-responders had scores of 3 (minimally improved) or worse. CGI scores were based on all available data including clinician and patient judgments, patient self-reports and clinician ratings. In addition, patients were asked to answer “yes” or “no” to two outcome questions before the blind was broken and the CGI was scored: 1) “Does the medication you’re taking in this study help with the problem you came here for?” and 2) “Do you want to continue taking what you’re taking?” A “yes” to both questions was necessary but not sufficient to define a responder on the CGI scale.

Secondary endpoints include the Fatigue Severity Scale, Epworth Sleepiness Scale, and Role Function Scale. The 9-item self-rated Fatigue Severity Scale (FSS),[24] measures the impact of fatigue on everyday functioning. Its internal consistency reliability is good (0.88–0.90) and it can detect change over time.[25] Scores for individual items range from 1 to 7; the final score is either the item average or total (we use total score with a cut-off of 41+ for eligibility). The Epworth Sleepiness Scale[26] inquires about the probability of dozing in various settings (0 = no chance; 3 = highly likely). Total scores are the item sum; range = 0 – 24.

The Role Function Scale includes 10 items drawn from the Short Form 36-item Health Survey (SF-36)[27] and other SF versions. It is intended to assess the extent to which fatigue has a behavioral impact on daily activities. Scores of frequency in the past week, on a 5 point scale, are summed with higher scores signifying greater role impairment.

In addition, we used the 7-item physical fatigue subscale of the Chalder Fatigue Scale[28] which assesses symptoms of fatigue in HIV+ patients. Likert response options range from 1 to 5, and items are summed for a total score.

Depression

In addition to the SCID modules for diagnosis of depressive disorders, we used the structured version of the 21-item Hamilton Rating Scale for Depression (HRSD).[29] The Beck Depression Inventory II (BDI)[30] is a 21-item self-report scale used to provide patient perspective on depressive symptoms. The CGI-Severity of Illness scale was also used to assess depression at baseline, and the 7-point Clinical Global Impressions- Improvement scale was used at all subsequent visits. The rating of “responder” at Week 4 was defined as a CGI Improvement score of “much improved” or “very much improved,” based on clinical interview, HRSD and BDI scores.

Side effects were measured at every study visit with a checklist modeled on SAFTEE (Systematic Assessment for Treatment Emergent Events).[31] A side effect was considered “treatment emergent” if the severity score (on a 6 point scale) at subsequent study visits was ≥ 2 points higher than baseline.

Neuropsychological Tests

A 1-hour battery of 10 neuropsychological tests represented the domains of verbal memory (WHO UCLA Verbal Learning Test,[32] Digit Span[33]), attention/speed of processing (WAIS-III Digit Symbol,[33] Color Trails 1,[34] Symbol Search[33]), executive function (Stroop,[35] Color Trails 2), cognitive flexibility (WAIS III Letter-Number Sequencing[33]), motor (Grooved Pegboard[36]), verbal fluency (Controlled Oral Word Association Test [37]) and reaction time (CALCap)[38].

Laboratory tests

Hematology, serum chemistry, thyroid panel, CD4 cell subsets, and HIV RNA viral load assay (detectable range, 50–100,000 copies) were performed at baseline, Week 4, Week 8 for placebo patients beginning armodafinil at Week 4, after 12 weeks on armodafinil, and for all patients at Week 26. Urine toxicology screens were performed at initial evaluation and at a random study visit. An EKG and cardiac history were performed to rule out mitral valve prolapse and left ventricular hypertrophy, based on an advisory from the manufacturer.

Statistical Analysis—Analyses include all patients who took at least one dose of study medication, including dropouts. Treatment group outcomes were analyzed with repeated measures analyses. Depression scales were first scored conventionally, and then adjusted scores without fatigue items were calculated. Treatment groups, and then responders and non-responders across treatments, were compared using X^2 tests and t tests for categorical and continuous variables, respectively. Following convention, $\log_{10}$ viral load was used, conservatively entering "1.69" when the result was "under 50 copies (= 1.70 $\log_{10}$ copies)" which was the assay's limit of detectability during the study. Paired t-tests were used to analyse temporal change in immune markers. All tests were 2-tailed, $\alpha = .05$.

RESULTS

(Note: all analyses are based on 70: Intention to Treat sample unless otherwise specified.)

Sample Characteristics

114 patients were screened for eligibility, 25 had medical or psychiatric exclusion criteria (e.g. bipolar or substance use diagnosis, medically unstable), 7 were active substance users, 4 were taking stimulants, 3 were not clinically fatigued, 5 patients declined participation, and 70 patients were randomized. Of these, 64 completed the 4-week trial. Randomized groups did not differ on any demographic, medical, psychiatric, cognitive or fatigue measures (Table 2). Mean age was 46 (range: 26–64), 87% were male, 49% were non-Hispanic white, 27% were black, 21% were Hispanic and 3%, other. Most had at least some college, although 11% (N=8) had not finished high school. 53% (N= 37) had a significant drug history but none had a current diagnosis of abuse or dependence, and 92% of the men were infected through sex with men.

At baseline, mean CD4 cell count was 490 (SD=220) and 57% of patients had an AIDS diagnosis according to CDC criteria based on history. They had known their HIV+ status for an average of 12 years (range: 4–276 months), 90% (N=63) were taking antiretroviral medications. 17% (N=12) had hepatitis C, and 44% (N=31) had a current (past month) Axis I depressive disorder. Twenty-nine patients (41%) were taking antidepressants.

Final Dose

Among completers randomized to armodafinil, final mean dose for responders was 219 (SD=40) mg/day, and for non-responders, 244 mg (SD= 17) mg/day (t = −2.75, 31.8df, p = .01). During the trial, maximum dose was 250 mg/day, but only for the last 2 days of the 4-week trial.

Cognitive Status at Baseline

Complete NP test data were available for 67 patients. Using the definition of 2+ SDs from the age and education-adjusted mean on 1+ non-redundant test, [39] 39% of patients (N = 26/67) met criteria for asymptomatic neurocognitive impairment (ANI), although none showed gross impairment in activities of daily living.

Treatment Outcome: Fatigue—At Week 4, 75% (27/36) of armodafinil patients were responders, compared to 26% (9/34) of placebo patients (X^2 =16.49, 1df, p < .0001, NNT = 2.1). As shown on Table 3, in repeated measures analyses, both fatigue measures (FSS and Chalder), Epworth Sleepiness Scale and Role Function Scale all showed superiority of armodafinil over placebo in reducing fatigue, although fatigue declined in both groups.

Responders did not differ from non-responders on any demographic variable. Women and men responded at comparable rates to armodafinil (80% or 4/5 vs.74% or 23/31, X^2 = .077, 1df, p = .78) although placebo response rates differed: 75% (3/4) for women and 20% (6/30) for men (X^2 = 5.49, 1df, p = .019. Response rate to armodafinil did not differ between those with and without ANI (75% vs. 74%, X^2 = .005, 1df, p = .94).

Fatigue responders and non-responders had equivalent baseline depression scores adjusted for fatigue; means were low in both groups. On the adjusted HRSD, means were 6.4 (3.7) and 6.2 (3.9) respectively (t = .263, p = .794); Adjusted BDI mean scores were 17.4 (9.3) vs. 17.0 (8.3) t = .157, (p = .876). Baseline fatigue measures also were unrelated to outcome.

Open Label treatment—Among the 27 armodafinil responders at Week 4, 24 patients completed 16 weeks of treatment; all maintained their response. Of the 9 armodafinil non-responders, 6 (who had shown partial response which was classified as “non-response”) continued on armodafinil, found it helpful, and completed the 16-week trial.

Among the 34 placebo patients, 6 dropped out, and 23 eventually had an open-label trial of armodafinil, of whom 16 (70%) were responders after 4 weeks of open label treatment. This includes 7 placebo responders who relapsed after the medication blind was broken, and 16 who were placebo non-responders. Cumulatively, 59 of the 64 study completers had a trial of armodafinil, with an overall response rate of 83% (49/59).

Week 26 Follow-Up

Fifty-six patients returned for a final assessment about 6 months after starting armodafinil. At this time, 33 (59%) patients continued to take armodafinil, either daily or as needed. Of the 23 who had discontinued its use, 9 were armodafinil non-responders, 3 said it was no longer needed, 6 could not get insurance coverage; and 5 had other explanations for not taking armodafinil.

Comparing self-report ratings at Week 26 for patients still taking armodafinil vs. those who were not, mean FSS score was lower (27 [SD= 10] vs. 40 [SD =13.8], t = 4.12, 53 df, p<.001). Mean adjusted BDI score for patients still taking armodafinil was also lower (4.7 [SD = 4.3]) vs. 12.9 [SD = 9.9] for patients not taking armodafinil (t = −4.21, 53df, p = .001). In

short, patients still taking armodafinil at Week 26 had less fatigue and fewer depressive symptoms.

Treatment Outcome: Depression

At study entry, 30 patients (43%) had an Axis I depression diagnosis excluding current major depression, of whom 14 were randomized to armodafinil and 16 to placebo. Combining those randomized to either treatment, 47% (N= 14) were rated responders in terms of both fatigue and depression, 10% (N= 3) reported improved fatigue but not depression, no patient reported improved mood in the absence of improved energy, while 43% (N= 13) did not improve in either domain. Thus, improvement (or no improvement) in fatigue and depression was concordant for 27 of 30 patients (90%). Outcome was concordant for 100% of the 14 depressed patients randomized to armodafinil: 12 (86%) reported improved energy and mood, and 2 (13%) reported no improvement of either.

Using repeated measures analyses to compare the 36 armodafinil patients vs. 34 placebo patients on depression measures, mean scores declined in both groups (Table 3). On the HRSD at baseline, mean scores in both groups were in the “not depressed” range, while for the BDI, the mean scores at baseline signified “moderate” depression. At Week 4, mean scores on both scales were in the “not depressed” range. There is some suggestion that armodafinil patients experienced greater mood improvement than placebo patients. Using repeated measures analyses, Week 4 HDRS scores declined more for the armodafinil than placebo groups ($F = 4.55$, $p = .037$) (Table 3). However, using adjusted mean scores from which the fatigue item was removed, the difference was no longer significant. BDI score changes did not differ between groups for either the original or fatigue-corrected scales: scores in both groups declined.

Safety of Armodafinil for HIV+ Patients

Effects on CD4 cell count and viral load: We monitored CD4 cell count and HIV RNA viral load on 5 occasions for patients who completed the entire trial: baseline, end of the double blind phase at Week 4; Week 8 for placebo patients starting armodafinil at Week 4; after 12 weeks on armodafinil, and at Week 26 when change from baseline in laboratory values was calculated for patients who continued on armodafinil vs. those who did not. Neither CD4 cell count nor viral load showed statistically or clinically significant changes in either direction in any comparison. Table 4 shows data for the Week 4 comparison between patients on armodafinil vs. placebo for illustrative purposes.

Treatment-emergent Side Effects: These were relatively uncommon and did not differ between treatment groups, perhaps due to slow dose titration (Table 5). Headache was most common, reported by 7 patients on armodafinil and 2 on placebo ($X^2 = 2.87$, $p = .09$). The lack of treatment-emergent irritability may be due to its prevalence at study entry when half the patients reported “moderate” or more severe problems. Two patients dropped out because of side effects; both had been randomized to placebo. Another patient ended treatment at Week 4 because at an effective dose, armodafinil made him too “hyper.” During the period of observation, no patient asked for higher doses once the protocol maximum of 250 mg/day was reached. Patients did not report rebound sleepiness or “crashing” when they skipped a dose.

DISCUSSION

As we found earlier for modafinil,[21] armodafinil appears effective in alleviating fatigue in HIV+ patients, with a large effect size compared to placebo (Number Needed to Treat [NNT] = 2.1)[40]. Response probably would have been greater had we achieved the maximum

dose earlier. Armodafinil was well tolerated, with few and transient adverse events; the most common was headache. Attrition was 9%; all dropouts had been randomized to placebo. Week 4 responders maintained their improvement throughout the 4-month study with no newly emergent adverse events. At Week 26, those still taking armodafinil had more energy and better mood than those who had stopped, replicating our earlier finding with modafinil. While there is theoretical evidence that modafinil (and thus armodafinil) has some potential for abuse,[41] we saw no evidence of craving, dependence, or dose escalation after initial response.

As in our RCT of modafinil,[21] we found no independent antidepressant effect of armodafinil. For 90% (27/30) of patients with baseline depressive diagnoses, responses in terms of fatigue and depression were concordant: both or neither improved. However, mean scores on depression measures improved for both active and placebo groups.

We found no statistically or clinically significant changes from baseline for CD4 count or viral load at Week 4 between active and placebo groups, or in any analysis of change over time. We thus failed to replicate the finding, from our larger modafinil RCT, of a decline in viral load at Week 4 among patients randomized to modafinil but not placebo, or a decline at Weeks 12 and 26 for those continuing on active drug. However, we found no suggestions of any negative effect of armodafinil on these markers.

Armodafinil was well tolerated and effective for most study participants. Among the 23 patients whose initial goal was return to work once energy improved, who completed at least 8 weeks of active medication, and who were not already working fulltime at study entry, we found that 8 had made no effort to do so, 4 had taken some steps, and 11 (48%) had succeeded in finding work, full-time or part-time, paid or volunteer. None cited the ongoing economic recession as the reason they failed to return to work.

Study limitations include the following: patients were seen at a single site in an urban setting, and all had access good medical care. The sample is relatively small. Women were underrepresented, and we excluded otherwise eligible patients with current substance use disorders or bipolar spectrum disorder. In addition, the protocol had 14 other exclusion criteria for safety reasons (Table 1) requiring laboratory and clinical screening, which limits generalizability. In clinical settings, however, care providers would already know their patient's medical and psychiatric history and status, so that such screening would not be necessary to determine appropriateness of armodafinil.

In summary, armodafinil was widely effective and well tolerated. Side effects were few, there was no evidence of tolerance, and patient acceptance was the rule.

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Table 1

Inclusion and Exclusion Criteria

Inclusion
HIV+
Ages 18–70
Clinically significant fatigue (Fatigue Severity Scale score >40)
Primary care provider approves study participation
Exclusion
Unstable medical condition
Change in antiretroviral medications within the past month
Untreated hypogonadism, hypothyroidism, anemia, hypertension
Untreated or under treated major depressive disorder
Initiated antidepressant medications within the past 2 months
Initiation of steroids within the past 6 weeks
Significant untreated insomnia
History of non-substance induced psychosis or bipolar disorder
Current/recent (past 4 months) substance use disorder
Currently taking psychostimulant medication
Left ventricular hypertrophy or symptomatic mitral valve prolapse

Table 2

Baseline Demographic, Medical and Psychiatric Characteristics of Study Patients (N = 70)

	ALL N = 70	Armodafinil N = 36	Placebo N = 34	t or X^2	*p*
Demographic					
Age, mean (SD) range	46 (8.4) 26–64	46 (8.7)	46 (8.2)	0.220	.826
Ethnicity, number (%)					
Black	19 (27%)	12 (33%)	7 (21%)		
White (non-Hispanic)	34 (49%)	17 (47%)	17 (50%)	1.860	.602
Hispanic	15 (21%)	6 (17%)	9 (27%)		
Other	2 (3%)	1 (3%)	1 (3%)		
Gender – Men, Number (%)	61 (87%)	31 (86%)	30 (88%)	0.070	.791
Men who have sex with men, number (%)	56 (80%)	31 (86%)	25 (74%)	1.730	.188
Years Education, mean (SD)	14.6 (2.7)	14.8 (2.7)	14.4 (2.8)	−0.696	.489
Work Status, number (%)					
Full time	9 (13%)	6 (17%)	3 (9%)		
Part time	11 (16%)	6 (17%)	5 (15%)	1.115	.573
Unemployed	50 (71%)	24 (67%)	26 (77%)		
Psychiatric					
DSM-IV depression diagnosis[1], number (%)	30 (43%)	14 (39%)	16 (47%)	0.477	.490
Taking antidepressant medication, number (%)	29 (41%)	15 (42%)	14 (41%)	0.002	.967
Past substance use disorder, number, (%)[2]	37 (53%)	19 (53%)	18 (53%)	<.0001	.989
Asymptomatic neurocognitive impairment, number (%)[3]	26 (39%)	12 (34%)	14 (44%)	0.631	.427
HRSD[4] adjusted for fatigue, mean (SD)	6.3 (3.8)	6.2 (3.7)	6.5 (3.9)	0.304	.762
BDI-II[5] adjusted for fatigue, mean (SD)	17.2 (8.8)	17.3 (8.2)	17.1 (9.4)	−0.103	.918
Fatigue Severity Scale, mean (SD)	52.8 (6.5)	52.6 (6.1)	53.1 (6.9)	0.344	.732
Chalder Fatigue Scale, mean (SD)	31.8 (4.4)	31.4 (4.6)	32.3 (4.2)	0.781	.438
Epworth Sleepiness Scale, mean (SD)	14.3 (4.7)	14.6 (5.1)	14.0 (4.4)	−0.516	.607
Role Function Scale, mean (SD)	37 (6.8)	36.2 (5.7)	37.8 (7.8)	0.981	.330
Medical					
Months since testing HIV+, mean (SD)	139.1 (79.1)	126.3 (84.3)	152.7 (72.0)	1.404	.165
AIDS Diagnosis, number, (%)	40 (57%)	19 (53%)	21 (62%)	0.577	.448

	ALL N = 70	Armodafinil N = 36	Placebo N = 34	t or X^2	*p*
Taking antiretroviral therapy, number, (%)	63 (90%)	32 (89%)	31 (91%)	0.102	.750
Hepatitis C, number, (%)	12 (17%)	5 (14%)	7 (21%)	0.553	.457
CD4 cell count, mean (SD)	498 (230)	519 (215)	476 (246)	−0.777	.440
Log_{10} Viral Load, mean (SD)	2.26 (0.95)	2.17 (0.81)	2.37 (1.12)	0.819	.416

[1] DSM-IV depression diagnosis of major depressive disorder in partial remission, minor depression, or dysthymia

[2] in partial or full remission >4 months

[3] The neuropsychological test battery was completed by 67 patients: 32 randomized to Armodafinil, 35 to placebo

[4] Hamilton Rating Scale for Depression

[5] Beck Depression Inventory-II

Table 3

Repeated Measure Analyses of Fatigue and Depression Measures

	Armodafinil		Placebo			
Measure	**Baseline**	**Week 4**	**Baseline**	**Week 4**	**F**	**P**
Fatigue Severity Scale	52.6 (6.13)	25.8 (14.23)	53.1 (6.87)	39.4 (14.91)	15.20	<.001
Chalder Fatigue Scale	31.4 (4.56)	18.9 (7.75)	32.3 (4.21)	25.3 (8.43)	7.95	.006
Epworth Sleepiness Scale	14.6 (5.05)	7.2 (4.37)	14.0 (4.39)	9.4 (5.19)	5.07	.028
Role Function Scale	36.2 (5.75)	19.9 (8.11)	37.8 (7.81)	28.3 (10.19)	7.06	.010
HRSD[1]	8.1 (3.60)	2.4 (2.79)	8.4 (3.99)	4.76 (3.60)	4.55	.037
Adjusted HRSD	6.2 (3.66)	1.8 (2.33)	6.5 (3.94)	3.4 (3.18)	2.22	.141
BDI[2]	20.6 (9.0)	9.8 (8.39)	20.4 (9.51)	12.6 (9.88)	2.19	.144
Adjusted BDI	17.3 (8.24)	8.9 (7.81)	17.1 (9.43)	10.9 (9.09)	1.42	.238

[1] Hamilton Rating Scale for Depression

[2] Beck Depression Inventory-II

Table 4

CD4 cell count and log_{10} viral load: double blind phase, paired t-tests within group

Measure	Group	Baseline	Week 4	df	t	p
CD4 cell count, Mean (SD)	Armodafinil	502 (202)	503 (224)	34	−.050	.960
	Placebo	450 (241)	445 (255)	26	.249	.805
Log_{10} HIV RNA viral load, Mean (SD)	Armodafinil	2.17 (.81)	2.15 (.87)	35	.310	.758
	Placebo	2.39 (1.13)	2.24 (1.07)	26	1.84	.077

Table 5

Patients Reporting Treatment Emergent Side Effects at Visit Weeks 1 – 4

Side Effect	All Patients (N = 70)	Armodafinil (N = 36)	Placebo (N = 34)	X^2 (df = 1)	*p*
Headache, N (%)	9 (13%)	7 (19%)	2 (6%)	2.87	.09
Nervousness, N (%)	5 (7%)	2 (6%)	3 (9%)	.282	.596
Insomnia, N (%)	4 (6%)	1 (3%)	3 (9%)	1.19	.276
Nausea, N (%)	3 (4%)	1 (3%)	2 (6%)	.411	.522
Irritability, N (%)	0	0	0	-	-