Modafinil Treatment for Fatigue in HIV/AIDS: A Randomized Placebo-Controlled Study

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Objective: To evaluate the efficacy and safety of modafinil in the treatment of fatigue in patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and to assess effect on depressive symptoms.

Method: Patients who were HIV+ and had clinically significant fatigue (according to the Fatigue Severity Scale [FSS]) were included in a 4-week randomized, placebo-controlled, double-blind trial. This was followed by an additional 8 weeks of open-label treatment for modafinil responders and 12 weeks for placebo nonresponders. The primary outcome measure for fatigue and depression was the Clinical Global Impressions-Improvement scale, supplemented by the FSS, Hamilton Depression Rating Scale, and Beck Depression Inventory. Safety was assessed with assays of CD4 cell count and HIV ribonucleic acid (RNA) viral load. Visits were weekly for 4 weeks, then biweekly, with a follow-up visit at 6 months. Maximum trial dose of modafinil was 200 mg/d. Data for this study were collected between December 2004 and December 2008.

Results: 115 patients were randomly assigned. In intention-to-treat analyses, fatigue response rate to modafinil was 73% and to placebo, 28%. Attrition was 9%. Modafinil did not have an effect on mood alone in the absence of improved energy. At week 4, CD4 cell counts did not change significantly; HIV RNA viral load showed a trend decline for patients taking modafinil but not for those taking placebo. At 6 months, those still taking modafinil had more energy and fewer depressive symptoms than patients who were not taking modafinil, and only those still taking modafinil showed a significant decline from baseline in their HIV RNA viral load.

Conclusions: Modafinil appears to be effective and well tolerated in treating fatigue in HIV+ patients. Consideration of its use is warranted considering the high prevalence of fatigue in the HIV community, its minimal side effects, and overall patient acceptance.

Trial Registration: clinicaltrials.gov Identifier: NCT00118378

J Clin Psychiatry 2010;71(6):707–715

Submitted: *February 25, 2009; accepted May 15, 2009.*
Online ahead of print: *May 4, 2010 (doi:10.4088/JCP.09m05171bro).*
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Fatigue is a common and clinically significant problem for many people with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). Prevalence estimates range from about 30%–50%,[1–3] depending on method of elicitation, and fatigue often has substantial behavioral impact. For example, Justice et al[4] found that fatigue was reported by two-thirds of 808 HIV-positive (HIV+) respondents and was strongly associated with functional limitations. Since fatigue is associated with restricted activity levels, it contributes to social isolation and consequent reduction in exposure to pleasant events and positive mood.[5–7] It is a common reason for leaving work as well as a barrier to reemployment, even when medical status is stable. In our group's analysis of correlates of employment among 141 HIV+ men,[8] unemployed men reported significantly more fatigue than those who worked. Together with other symptoms, fatigue may also interfere with medication adherence, including doses missed for reasons such as falling asleep prematurely or sleeping through a scheduled dose.[9–11] Overall, fatigue is prevalent, persistent, and can be disabling.

Fatigue may have multiple and overlapping etiologies, ranging from comorbid medical conditions, such as anemia and malnutrition,[12] hypogonadism,[13] hypothyroidism, and hepatitis C,[14] to medication side effects, including some antiretrovirals, some antidepressants, and pain medications. The preponderance of the available evidence does not support a relationship between level of immunosuppression and fatigue, since several studies have failed to find an association with CD4 cell count or HIV ribonucleic acid (RNA) viral load,[6,15] and prevalence rates have remained stable between the periods before and after the advent of combination antiretroviral medication.[16]

The substantial overlap between fatigue and depression is to some extent circular in that fatigue is 1 of the 9 criteria to diagnose major depressive disorder and dysthymia in *DSM-IV*[17] and is also associated with complaints such as poor concentration, which is another *DSM-IV* criterion for depression. There may be a reverse causal direction as well: when fatigue restricts activities and exposure to pleasant events, reduces social interactions, and leads to long days alone at home, dysphoric mood is a likely consequence. While the 2 conditions are associated,[18–20] fatigue may be present in the absence of depression.[1,21] Several treatments have been evaluated for fatigue in HIV+ patients, including methylphenidate and pemoline,[22] and dextroamphetamine.[23] Our group found that testosterone was more effective than fluoxetine or placebo for men presenting with

fatigue as well as depression.[24] While useful, these treatments have significant limitations regarding access, sustainability, and tolerance.

Modafinil is a schedule IV agent approved for treatment of narcolepsy, obstructive sleep apnea, and shift work–related sleep disorders. Its exact mechanism of action remains unknown. As summarized by Ballon and Feifel, the mechanisms "are 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."[25(p555)] Modafinil-induced neuronal activation is more localized to wakefulness areas compared to amphetamine-induced neuronal activation.[26]

Modafinil has been used with some success to treat fatigue in other medical conditions, including cancer,[27] multiple sclerosis,[28] and amyotrophic lateral sclerosis.[29] Findings have been inconsistent in studies of patients with Parkinson's disease.[30] In addition, our group conducted an open-label pilot study with 30 HIV+ patients and found an 85% response rate.[31]

Modafinil also has been used to treat residual depressive symptoms. In open-label studies, adjunctive modafinil was reportedly effective in alleviating fatigue in patients being treated for depression,[32,33] but modafinil was not superior to placebo in a controlled trial in its mood effects.[34] In a chart review of patients with major depression who took modafinil as monotherapy or as antidepressant augmentation, Beck Depression Inventory and Hamilton Depression Rating Scale (HDRS) scores showed a statistically significant decline after 3 months, although they were still in the symptomatic range.[35] We are not aware of placebo-controlled clinical trials of modafinil monotherapy for unipolar depression. However, a placebo-controlled trial was conducted for 85 patients with bipolar depression who were inadequately responsive to mood stabilization with or without adjunctive antidepressants.[36] More patients taking modafinil than those taking placebo showed a 50% decline of depressive symptoms. Apart from this study of bipolar depression, the limited available data are at best suggestive regarding antidepressant efficacy.

Because the package insert of modafinil refers to a potential "mild inducer effect" and because modafinil shares the same P450 metabolic pathway as some antiretroviral medications, safety was a significant consideration in this study. Since modafinil side effects are dose related, we limited maximum dose during the trial to 200 mg/d (the usual starting dose is 200 mg/d increasing to 400 mg/d) with slow dose titration. In addition, we monitored the surrogate markers of CD4 cell count and HIV RNA viral load at baseline, week 4, after 12 weeks on modafinil, and at week 26. While CD4 cell counts seldom change rapidly, viral load copies can show major changes within days. Since modafinil reaches steady state within 3 weeks, the week 4 assay was expected to capture changes, if any, due to direct drug effect or to potential interactions with the antiretroviral regimen, and the subsequent assays were intended to show longer range effects, if any.

Table 1. Inclusion and Exclusion Criteria for Patients Entering Trial of Modafinil for the Treatment of Fatigue

Inclusion criteria
HIV+
Aged 18–70 y
Clinically significant fatigue (Fatigue Severity Scale score >40)
Primary care provider approved study participation
Exclusion criteria
Unstable medical condition
Untreated hypogonadism, hypothyroidism, anemia, hypertension
Untreated or undertreated major depressive disorder
Initiated antidepressant medications within the past 6 weeks
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

On the basis of available findings, we conducted a randomized, double-blind, placebo-controlled trial of modafinil for the treatment of fatigue to assess its efficacy, mood effects, and safety. Study questions were (1) Is modafinil superior to placebo in ameliorating symptoms of fatigue? (2) Is modafinil 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 randomly assigned to modafinil versus placebo?

METHOD

Sample

Eligible patients were HIV+ and aged 21–75 years, had clinically significant fatigue, defined as interference with at least 2 daily activities on a Role Function Scale, adapted from the 36-item Short Form Health Survey,[37] and a score of at least 41 on the Fatigue Severity Scale (FSS). 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. 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 tests was administered. Neuropsychological test results are reported elsewhere.[38] Week 4 responders to modafinil were offered an additional 8 weeks of open-label medication, and placebo nonresponders or placebo responders who relapsed were offered open-label modafinil for 12 weeks. Modafinil nonresponders had their study medication stopped and returned 1 week later to consider alternative treatments (eg, methylphenidate) as clinically indicated. Placebo responders were followed without treatment. At the final study visit, patients were given prescriptions for modafinil and assistance was provided

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for those whose insurance companies required prior authorization or appeals. All patients were seen for a final follow-up visit at 6 months after initiation of modafinil, when energy, mood, activity level, and CD4 cell count and viral load were again assessed.

Patients were randomly assigned in blocks of 4 according to a computer-generated list provided by the New York State Psychiatric Institute Research Pharmacy (New York City), which also packaged study medications. Active and placebo modafinil were identical in appearance. Medication was dispensed by the study psychiatrist (R.R.) at each visit, and patients were asked to return unused tablets at the next visit. Starting dose was 50 mg/d, increased weekly in the absence of clinical response and dose-limiting side effects to a maximum of 200 mg/d in the double-blind trial. This schedule was based on both safety consideration and pilot work suggesting that patients were particularly sensitive to modafinil effects because of either concurrent medications or HIV infection itself. In the last year of the study, after reviewing cumulative safety data, patients with a partial response had the option of dose increase to 300 mg/d during open-label treatment.

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. Blood work (described below) was performed, and a letter was faxed to their HIV specialist describing the study and requesting a signed statement that there were no medical contraindications (eg, advanced liver disease) to the patient's study participation. Confirmed 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. Data were collected between December 2004 and December 2008.

Measures

Study eligibility criteria were evaluated with the Structured Clinical Interview for *DSM-IV* (SCID)[39] modules for depression to exclude major depressive disorder (MDD) and to identify current MDD in partial remission, minor depression, and dysthymia, which were permitted. Screens were used to identify (and exclude) patients with past or current psychotic conditions and bipolar disorder.

Fatigue. The primary endpoint defining responder versus nonresponder was the Clinical Global Impressions-Improvement scale (CGI-I).[40] Scores range from 1 = very much improved to 7 = very much worse. Responders were rated "1" or "2" on energy response compared to baseline; nonresponders had scores of 3 (minimally improved) or worse. This global assessment is based on all available data, including clinician judgment, patient self-reports, and ratings. Patients were asked to answer yes or no to 2 outcome questions before the blind was broken: (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?"

Secondary endpoints included the FSS[41] and Epworth Sleepiness Scale. Higher scores indicate more of the condition assessed. Nearly all modafinil trials have used the 9-item self-rated FSS, which is unidimensional and measures the impact of fatigue on everyday functioning. It has good psychometric properties (internal consistency reliability: 0.88–0.90) and can detect change over time.[42] 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+ to ascertain eligibility). The Epworth Sleepiness Scale[43] is also widely used in modafinil trials and inquires about the probability of dozing in various settings (0 = no chance; 3 = highly likely). Total scores are the item sum; range = 0–24.

In addition, we used the 7-item physical fatigue subscale of the Chalder Fatigue Scale,[44] which our group has previously found useful for assessing symptoms of fatigue in HIV+ patients. Higher scores reflect greater fatigue. 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 HDRS,[45] a clinician-rated scale to assess depressive severity, with scores combining severity and frequency. The Beck Depression Inventory-II (BDI-II)[46] is a 21-item self-report scale used to provide patient perspective on depressive symptoms. The Clinical Global Impressions-Severity of Illness scale[40] was used to assess depression at baseline, and the 7-point CGI-I was used at all subsequent visits. The primary measure of depression outcome to define *responder* was a CGI-I score of "much improved" or "very much improved," based on clinical interview and HDRS and BDI-II scores.

Side effects were measured at every study visit with a checklist modeled on the Systematic Assessment for Treatment Emergent Events,[47] a comprehensive assessment of treatment-emergent side effects. Each item, if present, is scored on a 5-point severity scale. A side effect was considered "treatment emergent" if the severity score at subsequent study visits was ≥ 2 points higher than at baseline.

Neuropsychological tests. A 1-hour battery of 10 neuropsychological tests represented the domains of verbal memory (World Health Organization–University of California, Los Angeles Verbal Learning Test[48]; Digit Span[49]), attention/speed of processing (Weschler Adult Intelligence Scale-III [WAIS-III] Digit Symbol,[49] Color Trails 1,[50] Symbol Search[49]), executive function (Stroop,[51] Color Trails 2), cognitive flexibility (WAIS-III Letter-Number Sequencing[49]), motor (Grooved Pegboard[52]), verbal fluency (Controlled Oral Word Association Test[53]) and reaction time (California Computerized Assessment Battery[54]).

Laboratory tests. The laboratory tests included hematology, serum chemistry, thyroid panel, CD4 cell subsets, and an HIV RNA viral load assay (detectable range, 50–100,000 copies). They were performed at baseline and week 4, at week 8 for placebo patients beginning modafinil at week 4, end of 12 weeks for patients taking modafinil, and at week 26 for all patients. Clinically significant change was defined as a change of ≥ 100 cells in CD4 cell count or ≥ 0.5 $\log_{10}$ in viral load copies. While CD4 cell counts seldom change rapidly, viral load copies can show major changes within days.[55] Since modafinil reaches steady state within 3 weeks, the week 4 assay was expected to capture change, if any, due to drug interactions. Urine toxicology screens were performed at initial evaluation and at a random study visit. In the final study year, an electrocardiogram and cardiac history were added to the screening procedures to rule out mitral valve prolapse and left ventricular hypertrophy, based on an advisory from the manufacturer.

Statistical Analysis

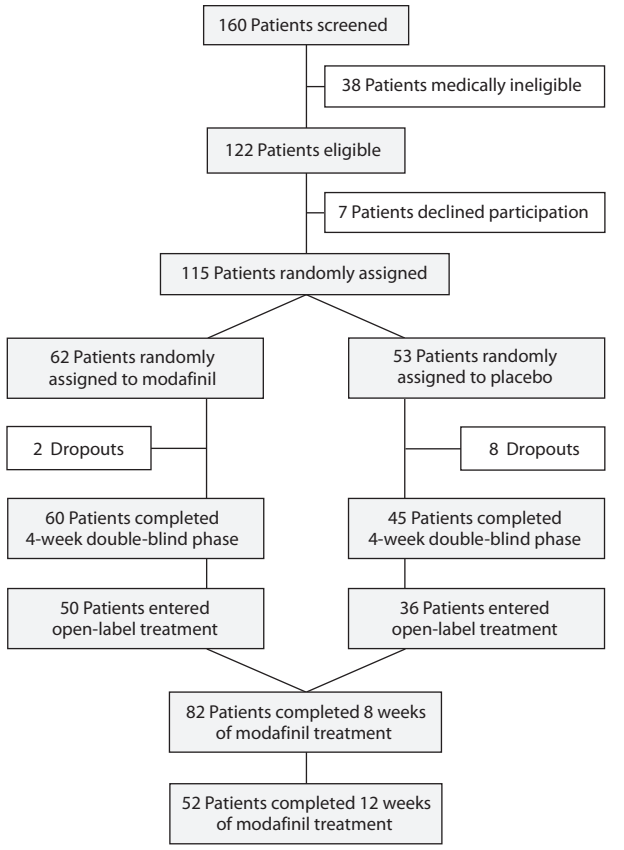
Analyses include all patients who took at least 1 dose of study medication, including dropouts. We did not perform separate analyses for completers only. Treatment group outcomes were analyzed with repeated-measures analyses. Responders and nonresponders were compared using χ^2 tests and *t* tests for 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 analyze temporal change in immune markers. All tests were 2-tailed, $\alpha = .05$.

RESULTS

Sample Characteristics

All analyses are base on N = 115, intention-to-treat sample, unless otherwise specified. As shown in Figure 1, one hundred sixty patients were screened for eligibility, 38 had medical or psychiatric exclusion criteria (eg, bipolar or substance use diagnosis, medically unstable), 7 patients declined participation, and 115 patients were randomly assigned. Of these, 10 dropped out, all within the first 2 weeks. Among dropouts, 8 were on placebo. Reasons included side effects (n = 2, both on placebo), drug relapse (n = 3), or other reasons unrelated to the study, and 105 completed the 4-week trial. Randomized groups did not differ significantly on any demographic, medical, depression, cognitive or fatigue measures (Table 2). Mean age was 46 years (SD = 9; range, 24–70), 87% were male, 39% were black, 34% were non-Hispanic white, 25% were Hispanic, and 2% were of another ethnic background. Most had at least some college, although 19% had not finished high school. Fifty percent (n = 57) had a significant drug history, but none had a current diagnosis of abuse or dependence, and 72% (n = 83) were men who had sex with men.

Figure 1. Trial Patient Flowchart



At baseline, mean CD4 cell count was 471 (SD = 254), and 62% of patients had an AIDS diagnosis according to CDC criteria[56] based on history, although only 13% had current AIDS-related medical conditions. They had known their HIV+ status for a mean of 12 years (range, 2–264 months), 89% (n = 102) were taking antiretroviral medications, 19% (n = 22) had hepatitis C, and 42% (n = 48) had a current (past month) depressive disorder, including dysthymia, major depression in partial remission, or minor depression (3 or 4 of the 9 *DSM-IV* MDD criteria). Twenty-nine percent (n = 33) were taking antidepressants.

Final dose. Among completers, final mean dose for responders was 183 (SD = 39) mg/d, and for nonresponders, 190 (SD = 31) mg/d ($t_{113} = -0.44$, $P = .66$). During the trial, the maximum dose was 200 mg/d at week 4. In the last year of the study, 5 patients with time-limited response had their dose increased to 300 mg/d: 200 mg in the morning and 100 mg at midday to extend duration of effect.

Cognitive status at baseline. Complete neuropsychological test data were available for 103 patients. Using current research nosology for HIV-related neurocognitive impairment,[57] 78% of patients (n = 80) met criteria for asymptomatic neurocognitive impairment (ANI) and 1 patient informed us he had a diagnosis of dementia based on a brain magnetic resonance imaging scan, but he did not meet current criteria for HIV-associated dementia in terms of neuropsychological test performance

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Table 2. Baseline Demographic, Medical, and Psychiatric Characteristics of Study Patients (N = 115)

Characteristic	All, N = 115	Modafinil, n = 62	Placebo, n = 53	t or χ^2	P
Demographic					
Age, mean (SD), y	46 (9)	46 (9)	46 (9)	−0.119	.906
Age, range, y	24–70				
Ethnicity, n (%)					
Black	45 (39)	23 (37)	22 (42)	0.613	.894
White (non-Hispanic)	39 (34)	23 (37)	16 (30)		
Hispanic	29 (25)	15 (24)	14 (26)		
Other	2 (2)	1 (2)	1 (2)		
Gender, n (%)					
Men	100 (87)	54 (87)	46 (87)	0.002	.961
Women	15 (13)	8 (13)	7 (13)		
Years of education, mean (SD)	14 (3)	14 (3)	14 (3)	0.384	.702
Work status, n (%)					
Full time	14 (12)	10 (16)	4 (8)	3.252	.197
Part time	19 (17)	12 (19)	7 (13)		
Unemployed	82 (71)	40 (65)	42 (79)		
Men who have sex with men, n (%)	83 (72)	45 (73)	38 (72)	0.011	.916
Psychiatric					
DSM-IV depression diagnosis,[a] n (%)	48 (42)	27 (44)	21 (40)	0.181	.670
Past drug use history, n (%)	57 (50)	33 (53)	24 (45)	0.721	.396
HDRS score adjusted for fatigue, mean (SD)	7 (4)	8 (4)	7 (5)	−0.979	.330
BDI-II score adjusted for fatigue, mean (SD)	17 (9)	17 (9)	16 (9)	−1.014	.313
Fatigue Severity Scale score, mean (SD)	52 (6)	52 (6)	52 (7)	−0.170	.865
Chalder Fatigue Scale score, mean (SD)	32 (5)	32 (5)	32 (5)	−0.250	.803
Epworth Sleepiness Scale score, mean (SD)	14 (5)	14 (5)	14 (5)	−0.240	.810
Asymptomatic neurocognitive impairment, n (%)[b]	80 (78)	45 (76)	35 (80)	0.156	.690
Medical					
Months since testing HIV+, mean (SD)	140 (70)	134 (69)	148 (70)	1.040	.301
AIDS diagnosis, n (%)	71 (62)	39 (63)	32 (60)	0.077	.781
Taking antiretroviral therapy, n (%)	102 (89)	55 (89)	47 (89)	< 0.001	.996
Hepatitis C, n (%)	22 (19)	11 (18)	11 (21)	0.168	.682
CD4 cell count, mean (SD)	471 (254)	486 (250)	449 (261)	−0.724	.470
Log_{10} viral load, mean (SD)	2.46 (1.16)	2.50 (1.15)	2.41 (1.19)	−0.406	.686

[a] *DSM-IV* depression diagnosis of major depressive disorder in partial remission, minor depression, or dysthymia.
[b] Neurpsychological tests were completed by 103 subjects, 59 in the modafinil group and 44 in the placebo group.
Abbreviations: AIDS = acquired immune deficiency syndrome, BDI-II = Beck Depression Inventory-II, HDRS = Hamilton Depression Rating Scale, HIV = human immunodeficiency virus.

or interference with activities of daily living attributable to cognitive impairment.

Treatment Outcome: Fatigue (intention to treat)

At week 4, 73% (45/62) of patients randomly assigned to modafinil were responders based on CGI-I scores, compared to 28% (15/53) of patients randomly assigned to placebo ($\chi^2_1 = 22.45$, $P < .0001$, number needed to treat [NNT] = 2.3). As shown in Table 3, in repeated-measures analyses, all fatigue measures showed superiority of modafinil over placebo in reducing fatigue, although fatigue improved in both groups.

Responders did not differ from nonresponders on any demographic variable. Women and men responded at comparable rates to modafinil (63% or 5/8 vs 74% or 40/54, $\chi^2_1 = 0.469$, $P = .49$) and placebo response rate (28% for both). Response rate for the 22 patients with hepatitis C was similar to that of hepatitis C–negative patients in the total sample: 64% of hepatitis C–positive patients and 50% of hepatitis C–negative patients were responders ($\chi^2_1 = 1.43$, $P = .23$). All 11 hepatitis C–positive patients randomly assigned to modafinil were responders versus 67% of hepatitis C–negative patients ($\chi^2_1 = 5.05$, $P = .025$). Response rate to modafinil did not differ between those with and without ANI (76% vs 64%, $\chi^2_1 = 0.686$, $P = .41$), although no patients without ANI responded to placebo compared to 37% of ANI patients who did ($\chi^2_1 = 4.745$, $P = .029$). Response rates did not differ by race/ethnicity ($\chi^2_3 = 2.48$, $P = .48$).

Responders had slightly higher mean HDRS scores adjusted for fatigue, although both means were low (8 [SD = 5] vs 6 [SD = 4], $t = 2.48$, $P = .015$); BDI-II mean scores did not differ. Baseline fatigue measures were unrelated to outcome. There was no difference in response to modafinil between patients with and without asymptomatic neurocognitive impairment ($\chi^2_1 = 0.69$, $P = .41$). The only distinguishing medical variable was percentage with an AIDS diagnosis, which showed a trend to higher proportion among nonresponders versus responders(71% vs 53%, $\chi^2_1 = 3.75$, $P = .053$).

Open-Label Treatment

Among 62 patients randomly assigned to modafinil, 2 were dropouts, 44 were responders, and 16 were nonresponders at week 4. Forty responders completed 8 weeks of modafinil treatment and maintained their response. Of the nonresponders, 5 ended the study and did not return, 4 were treated with another stimulant medication, and

Table 3. Repeated-Measures Analyses of Fatigue Scale Scores at Baseline and Week 4 for Modafinil and Placebo Groups

	Modafinil (n = 62)		Placebo (n = 53)			
Measure	Baseline	Week 4	Baseline	Week 4	*F*	*P*
Fatigue Severity Scale, mean (SD)	52 (7)	34 (5)	52 (6)	43 (13)	13.05	< .001
Chalder Fatigue Scale, mean (SD)	32 (5)	22 (8)	32 (5)	26 (8)	5.01	.027
Role Function Scale, mean (SD)	39 (7)	22 (9)	36 (6)	27 (11)	14.90	< .001
Epworth Sleepiness Scale, mean (SD)	14 (5)	9 (5)	14 (5)	11 (6)	6.33	.013

7 decided modafinil was in fact helpful and resumed treatment, often adjusting the timing or increasing the dose to 300 mg/d; all 7 reported improved energy and completed an additional 8 weeks of modafinil treatment.

In addition to the 60 patients randomly assigned to modafinil who completed at least 4 weeks, 36 of the 53 placebo patients eventually had an open-label trial: 8 of the 13 "responders" who completed the 4-week trial relapsed and started modafinil, of whom 7 (88%) were responders. Twenty-eight of 32 placebo nonresponders who completed 4 weeks tried modafinil, of whom 21 (75%) were responders.

Week 26 Follow-Up

Ninety-seven patients returned for a final study visit about 6 months after starting modafinil. Among those we were able to contact, none declined this visit. Blood work was repeated, and fatigue, depression and behavior changes, if any, were assessed. At this time, 49 patients (50.5%) continued to take modafinil, either daily or as needed. Of the 48 who had discontinued its use, 16 were originally modafinil nonresponders, 6 said it was no longer needed, 9 could not get insurance coverage, and the remainder had a variety of other explanations for not taking modafinil.

When self-report ratings at week 26 for patients still taking modafinil were compared with those who were not, mean FSS score was lower (28 [SD = 3.5] vs 40 [SD = 13.4], $t_{92} = 4.09$, $P < .001$). Mean BDI-II score for patients still taking modafinil was also lower versus those patients not taking modafinil (6.6 [SD = 7.7]) vs 11.7 [SD = 9.7], $t_{93} = 2.82$, $P = .006$). In short, patients taking modafinil at week 26 had less fatigue and fewer depressive symptoms.

Treatment Outcome: Depression

At study entry, 48 patients (42%) had an Axis I depression diagnosis excluding current major depression, of whom 27 were randomly assigned to modafinil and 21 to placebo. Combining those randomly assigned to either treatment with a baseline CGI depression score of ≥ 3, 41% (n = 18) were rated responders in terms of both fatigue and depression, 23% (n = 10) reported improved fatigue but not depression, 4% (n = 2) reported improved mood but not fatigue, and 32% (n = 14) did not improve in either domain. Among the 26 patients randomly assigned to modafinil with a baseline depression diagnosis, and using CGI depression rating (≥ 3 signifies nonresponse) as the week 4 outcome measure, 15 (58%) reported improved energy and mood, 7 (27%) reported improved energy but not mood, 1 (4%) reported improved mood but not energy, and 3 (12%) reported no improvement in either. Overall, modafinil did not have an effect on mood alone in the absence of improved energy.

For the entire sample, depression measures did not show differential improvement for modafinil compared to placebo as shown in Table 3: mean scores declined for both groups. The same results were obtained using adjusted mean scores from which the fatigue items on each scale were deleted.

Safety of Modafinil 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 modafinil at week 4, end of 12 weeks for patients taking modafinil, and at week 26. Results are shown in Tables 4 and 5. While CD4 cell count did not show either statistically or clinically significant changes in either direction at any point, viral load showed a trend decline for patients taking modafinil versus placebo at week 4 and *diminished* significantly for all patients taking modafinil for 12 weeks and for patients still taking modafinil versus those who were not at week 26 when the difference of nearly 0.5 log approached clinical significance as well as statistical significance.

Treatment-emergent side effects. As shown in Table 6, treatment-emergent side effects were relatively uncommon and did not differ between treatment groups, perhaps due to our slow dose titration. Headache was most common, reported by 4 patients taking modafinil and 3 on placebo. Two patients dropped out because of side effects; both had been randomly assigned to placebo. Two other patients who were modafinil responders ended treatment after 4 weeks because the benefit did not outweigh side effects (anxious irritability, and [treated] fluctuating blood pressure). During the period of observation, dependence did not develop, nor did patients report rebound sleepiness or "crashing" if they skipped a dose or, in open-label treatment, selectively took modafinil on busy days. Modafinil appears to have a low potential for abuse, and need for dose escalation after initial response was rare, as elsewhere reported.[58]

Double-Blind Guesses

To determine whether the study doctor or the patients could penetrate the double-blind, each was asked to "guess" the treatment after ratings were completed

Table 4. CD4 Cell Count and Log_{10} Viral Load During Double-Blind and Open-Treatment Phases: Paired *t* Tests Within Groups[a]

	Double-Blind Phase					Open-Treatment Phase		
		Modafinil Group (n = 58)		Placebo Group (n = 44)			Modafinil, 12 Wk (n = 73)	
Measure	Week	Mean (SD)	Statistic	Mean (SD)	Statistic	Week	Mean (SD)	Statistic
CD4 cell count	0	481 (249)	$t = 0.85$	459 (257)	$t = -1.20$	0	475 (272)	$t = 1.79$
	4	466 (244)	$P = .40$	482 (240)	$P = .24$	12	444 (223)	$P = .08$
Log_{10} viral load	0	2.53 (1.2)	$t = 1.98$	2.41 (1.2)	$t = 1.05$	0	2.53 (1.19)	$t = 3.02$
	4	2.31 (1.0)	$P = .052$	2.30 (1.1)	$P = .300$	12	2.20 (0.99)	$P = .003$

[a]No statistically significant differences were found between groups on CD4 cell count and log_{10} viral load at baseline and week 4.

Table 5. CD4 Cell Count and Log_{10} Viral Load at 6-Month Follow-Up: Paired *t* Tests Within Groups

		Modafinil, 6 Mo (n = 47)		Not on Modafinil (n = 44)	
Measure	Week	Mean (SD)	Statistic	Mean (SD)	Statistic
CD4 cell count	0	463 (259)	$t = 1.04$	489 (267)	$t = 1.28$
	26	438 (181)	$P = .303$	451 (241)	$P = .207$
Log_{10} viral load	0	2.49 (1.18)	$t = 2.85$	2.51 (1.23)	$t = 0.35$
	26	2.05 (0.67)	$P = .007$	2.45 (1.26)	$P = .729$

Table 6. Patients Reporting Side Effects at Any Visit During Weeks 1–4

Side Effect, n (%)	All Patients (N = 115)	Modafinil (n = 62)	Placebo (n = 53)	χ^2_1	*P*
Headache	7 (6.1)	4 (6.5)	3 (5.7)	0.031	> .999
Insomnia	4 (3.5)	3 (4.8)	1 (1.9)	0.742	.623
Nausea	2 (1.7)	2 (3.2)	0	1.740	.499
Nervousness	1 (0.9)	1 (1.6)	0	0.862	> .999
Irritability	1 (0.9)	1 (1.6)	0	0.862	> .999

but before the blind was broken at week 4. Overall, the doctor guessed correctly 65% of the time (68% for modafinil and 60% for placebo). This is better than chance ($\chi^2_1 = 4.4$, $P < .05$). He was more accurate with modafinil responders (91%) than placebo responders (0%) for whom he always guessed "modafinil."

Patients' guesses were overall correct 66% of the time, including 63% of those who received modafinil and 69% of those who received placebo. This is also better than chance ($\chi^2_1 = 5.6$, $P = < .02$). Doctor and patient guesses were concordant 56% of the time overall: 53% for placebo patients and 58% for modafinil patients. It appears that both doctor and patients based their guesses on whether the patient's energy improved, since side effects were, in general, minimal.

DISCUSSION

Modafinil appears to be effective in alleviating fatigue in HIV+ patients, with a large effect size compared to placebo (NNT = 2.3).[59] Week-4 responders maintained their response through week 12 with no loss of effect or newly emergent adverse events. Adverse events were usually mild and transient.

In this trial, modafinil did not have an independent antidepressant effect in the absence of improved energy, which is consistent with the findings of modafinil augmentation in depression.[34] While mean scores on both depression measures (HDRS and BDI-II, adjusted for fatigue item) improved for patients randomly assigned to either modafinil or placebo, nearly all patients with baseline depression showed diminished depressive symptoms only if energy also improved.

It is exceedingly difficult to determine whether increased energy alone is responsible for the improvement in everyday functioning reported by the majority of patients or is also or instead associated with neurocognitive changes and/or alleviation of depressive symptoms. All 3 conditions—fatigue, neurocognitive impairment, and depression—are characterized by "diminished ability to think or concentrate" (a *DSM-IV* criterion for depression) and problems of focus and alertness. Disaggregating these possible effects is particularly challenging in this sample, given the prevalence at study entry of both non–major depressive disorders (42%) and asymptomatic cognitive impairment (78%) in addition to the mandatory eligibility criterion of "fatigue that interferes with everyday activities." Perhaps some clarity can be derived from the observation that patients without neurocognitive impairment reported the same rate of response to modafinil in terms of energy and stamina as did patients with ANI. Similarly, patients without depression responded to modafinil at the same rate as patients with depression. Nevertheless, we cannot conclusively attribute functional changes exclusively to restored energy.

Markers of immunologic and virologic status were monitored for safety reasons because of the theoretical possibility of an inducer effect of modafinil on antiretrovirals (hastening their metabolism and thus reducing potency), since both drug classes share the same metabolic pathway. Unexpectedly, we observed a statistically significant decline in viral load for patients randomly assigned to modafinil but not placebo at week 4, perhaps reflecting improved medication adherence. This decline in viral load was also observed after 12 weeks in patients on treatment with modafinil for those who had a full course of treatment and also at week 26 when we compared change from baseline for patients still taking modafinil; for those who were not, there was no decline in viral load from baseline.

Six months after starting modafinil, 97 patients were reevaluated. Among those still taking modafinil, as noted above, HIV RNA viral load had declined, as had self-rated fatigue and depressive symptoms compared to those who

were not taking modafinil. Thus, positive effects reported at week 4 were maintained at week 26.

Modafinil was widely considered helpful and effective in enabling participants to carry out activities of daily living that previously had been restricted by fatigue. Examples include cleaning one's house, going outside more often, taking walks, socializing, and otherwise being less isolated and limited. However, initiation or resumption of more complex goals was uncommon. Not all patients intended to study or work in the future, their decision based on health concerns; the "golden handcuffs" of needs-based benefits such as health insurance, which are lost upon return to paid employment; or age. Nevertheless, of those who initially aspired to return to work, take classes, or enroll in degree programs, only 16 of 71 (23%) met 1 of these goals by week 26, even though they initially stated that fatigue was the barrier preventing their attainment. It seems likely that additional support and tailored interventions are needed to assist HIV+ patients in achieving such goals, given months or years of inactivity and relative passivity in terms of daily living. Modafinil alone did not bring about widespread behavior change of this nature.

Study limitations include the conduct of the study at a single site in an urban setting where most patients have good access to medical care. Women were underrepresented despite outreach efforts. We also excluded otherwise eligible patients with current substance use disorders. The interesting finding of decreases in HIV RNA viral load associated with modafinil is a post hoc finding that requires replication. In this study, preservation of the double-blind was not fully achieved, although it has long been recognized that efficacy of the active drug and lack of efficacy of placebo may act as unblinding factors.[60] Finally, there was no supplementary intervention to support achievement of behavioral goals elicited at study entry once energy was restored.

A limitation in access to modafinil concerns insurance coverage. Its use for fatigue is off-label, and the medication is expensive (about $10/d for 200 mg, which is a common daily dose). Some insurers flatly deny coverage, while others require prior authorization, appeals, or sleep studies (to address possible indicated use for sleep disorders); these time-consuming procedures are difficult to conduct in busy HIV clinics with limited personnel.

In summary, modafinil was widely effective and well tolerated in this sample of patients with HIV/AIDS. While some HIV care providers are reluctant to prescribe it, since it is a controlled "psychoactive" substance, consideration of its use is warranted considering the high prevalence of fatigue among people with HIV/AIDS, its generally mild side effects, lack of development of tolerance, and overall patient acceptance.

Drug names: dextroamphetamine (Dexedrine and others), fluoxetine (Prozac and others), methylphenidate (Daytrana, Ritalin, and others), modafinil (Provigil).

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Potential conflicts of interest: None reported.
Funding/support: None reported.

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