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Changes in quality of life and sexual health are associated with low-dose peginterferon therapy and disease progression in patients with chronic hepatitis C

K. K. SNOW*, H. L. BONKOVSKY†, R. J. FONTANA‡, H.-Y. KIM*, R. K. STERLINGS§, A. M. DI BISCEGLIE¶, T. R. MORGAN**, J. L. DIENSTAG††, M. G. GHANY‡‡ & THE HALT-C TRIAL GROUP

*New England Research Institutes, Watertown, MA, USA; †Departments of Medicine and Molecular & Structural Biology and The Liver-Biliary-Pancreatic Center, University of Connecticut Health Center, Farmington, CT, USA; ‡Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA; §Hepatology Section, Virginia Commonwealth University Medical Center, Richmond, VA, USA; ¶Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St Louis, MO, USA; **Division of Gastroenterology, University of California – Irvine, Irvine, CA and Gastroenterology Service, VA Long Beach Healthcare System, Long Beach, CA, USA; ††Gastrointestinal Unit (Medical Services), Massachusetts General Hospital and the Department of Medicine, Harvard Medical School, Boston, MA, USA; ‡‡Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

Correspondence to:
Dr K. K. Snow, New England Research Institutes, 9 Galen Street, Watertown, MA 02472, USA.
E-mail: ksnow@neriscience.com

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SUMMARY

Background
Primary analysis of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial showed long-term peginterferon therapy did not reduce complications in patients with chronic hepatitis C and advanced fibrosis or cirrhosis.

Aim
To assess the effects of long-term peginterferon therapy and disease progression on health-related quality of life (HRQOL), symptoms and sexual health in HALT-C patients.

Methods
A total of 517 HALT-C patients received peginterferon alfa-2a (90 μg/week); 532 received no additional treatment for 3.5 years. Patients were followed up for outcomes of death, hepatocellular carcinoma and hepatic decompensation. Sexual health, SF-36 scores and symptoms were serially assessed by repeated-measures analyses of covariance.

Results
Patients with cirrhosis (n = 427) reported lower general well-being and more fatigue ($P < 0.001$) than patients with fibrosis (n = 622). Physical scores declined significantly over time, independent of treatment, and patients with cirrhosis reported lower scores. Vitality scores were lower in those with cirrhosis, and treated patients experienced a greater decline over time than untreated patients; HRQOL rebounded after treatment ended. Patients with a clinical outcome had significantly greater declines in all SF-36 and symptom scores. Among men, Sexual Health scores were significantly worse in treated patients and in those with a clinical outcome.

Conclusion
Clinical progression of chronic hepatitis C and maintenance peginterferon therapy led to worsening of symptoms, HRQOL and, in men, sexual health in a large patient cohort followed up over 4 years (NCT00006164).

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INTRODUCTION

Chronic hepatitis C (CHC) is a leading cause of chronic liver disease, liver failure and hepatocellular carcinoma (HCC) in the US and other Western countries.[1] Among the estimated 3.2 million adult Americans infected chronically with hepatitis C virus (HCV), many are unaware of their infections because they lack clinically apparent signs or symptoms.[2] With disease progression, however, patients may experience various nonspecific symptoms such as fatigue, nausea and right upper quadrant pain.[3–6] In addition, many patients with CHC report reduced quality of life although the relationship with disease severity is modest and at times inconsistent.[7–13] The weak correlation of liver disease severity and clinical symptoms with quality of life in patients with CHC may result, in part, from the influence of other commonly encountered medical and psychiatric comorbidities, such as diabetes mellitus and depression.[14, 15]

Several longitudinal studies of interferon therapy in patients with CHC have shown improvements in health-related quality of life (HRQOL) in patients who are able to achieve a sustained virological response (SVR) compared with nonresponders and relapsers.[10, 11, 16–35] Whether these improvements resulted from a sustained loss of viral replication or from the psychological improvement following the cure of a chronic disease and an improvement in prognosis remains unknown. Because of the slow rate of disease progression and the resultant need to follow a large number of patients prospectively for several years, none of these studies demonstrated an association between objective disease progression and worsening symptoms or HRQOL. Sexual dysfunction associated with CHC has also been reported,[36, 37] but the relationship between sexual dysfunction and disease severity or progression has not been well defined. Furthermore, psychological concerns about harbouring an infectious disease that can be transmitted to others may influence sexual health parameters in patients with CHC.

Recently, the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial demonstrated that maintenance peginterferon therapy did not reduce the rate of clinical or histological disease progression in patients with CHC and advanced fibrosis, with or without cirrhosis, who did not have a response to initial treatment with peginterferon and ribavirin.[38] During the trial, prospective assessment of symptoms and HRQOL was incorporated as a planned secondary outcome. We hypothesized that because of the side effect profile of interferon therapy, prolonged treatment with low-dose peginterferon would be difficult to tolerate and therefore associated with worsening fatigue, reduced general well being and reductions in HRQOL. In addition, we set out to measure the impact of maintenance peginterferon therapy on sexual health. We have previously shown that (i) HALT-C participants with cirrhosis had lower HRQOL scores than participants with noncirrhotic fibrosis at entry into the study and (ii) HALT-C participants who achieved an SVR after peginterferon/ribavirin therapy had improved HRQOL and Sexual Health scores.[22] The current analyses summarize the results of the assessment of symptoms, HRQOL and sexual enjoyment, desire, and function before, during and after the randomized phase of the trial, focusing on the effects of low-dose peginterferon therapy and disease progression.

PATIENTS AND METHODS

Patients

The design of the HALT-C Trial and its major outcomes have been described previously.[38, 39] Briefly, patients with CHC and advanced fibrosis, with or without cirrhosis, who had failed to respond to a previous course of antiviral therapy, were enrolled into the trial at 10 study centres in the US. Enrolment criteria included age of 18 years or older; the presence of HCV RNA in serum; failure to achieve an SVR with a previous adequate course of combination antiviral therapy; advanced hepatic fibrosis on liver biopsy (Ishak stage ≥ 3 fibrosis)[40] stratified into a noncirrhotic fibrosis group (stage 3 or 4) and a cirrhosis group (stage 5 or 6); no history of hepatic decompensation or HCC; and the absence of various exclusion criteria including uncontrolled medical or psychiatric conditions, interferon intolerance and active use of illicit drugs or alcohol abuse.[39]

After baseline evaluation, patients were retreated during a 'lead-in' phase with peginterferon alfa-2a (180 μg weekly; Pegasys; Roche Pharmaceuticals, Nutley, NJ, USA) and ribavirin (1000–1200 mg daily; Copegus; Roche). Patients with detectable serum HCV RNA levels at week 20 were classified as nonresponders and were randomized at week 24 into either the maintenance-therapy group (90 μg of peginterferon alfa-2a

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weekly without ribavirin) or the untreated control group. Patients with undetectable serum HCV RNA at week 20 continued therapy for 48 weeks.[41] If HCV RNA was detected again after week 20, either during treatment (breakthrough) or after cessation of treatment (relapse), the patient was offered the opportunity to undergo randomization into the HALT-C Trial ('breakthrough or relapse' cohort). During the trial, the protocol was amended to allow patients who had failed treatment with peginterferon plus ribavirin outside the study to undergo randomization ('express' cohort). Treatment ceased per protocol at study month 48.

Study endpoints

Primary clinical outcomes included death, hepatic decompensation (variceal haemorrhage, ascites, spontaneous bacterial peritonitis or hepatic encephalopathy), HCC, a Child–Turcotte–Pugh score[42] of ≥7 on two consecutive study visits and for patients with noncirrhotic fibrosis at baseline, an increase in the Ishak fibrosis score of ≥2 points according to assessment of liver-biopsy specimens obtained during the study.

During the randomized phase of the trial, patients were seen every 3 months to obtain a medical history, physical examination and laboratory testing to monitor the effects of peginterferon therapy and to assess for clinical endpoints and adverse events. The patients underwent hepatic ultrasound every 12 months to screen for HCC, as well as liver biopsy at baseline and study months 24 and 48. After trial completion at study month 48, patients were followed up at 6-month intervals. The study was approved by local institutional review boards and all patients provided written informed consent.

HRQOL and sexual health questionnaires

To measure HRQOL, we administered the highly reliable and validated Short Form Health Survey (SF-36)[43] at annual study visits. The SF-36 Physical and Mental Summary scales (0 = worst; 100 = best) are standardized around a population mean score of 50. Observed differences of three points or greater on the measured scales are considered clinically significant.[44] Three questions that addressed self-reported sexual satisfaction and enjoyment, desire and interest, and functioning and performance were added to the SF-36 (Appendix A). The composite Sexual Health Scale was calculated as the mean of completed items in the scale (0 = worst; 100 = best) and was not adjusted to reflect a population mean.[22]

Symptom questionnaire

We asked study patients to rank their clinical symptoms on a self-administered 10-cm visual analogue scale, with the score equalling the measured distance from the 0-cm left mark (Appendix A).[45] For these analyses, we analysed the baseline and annual symptom scores for fatigue (none = 0 cm to worst ever = 10 cm) and general well-being ('how you feel overall', very good = 0 cm to very bad = 10 cm).

Data analyses

Statistical analyses were performed at the Data Coordinating Center (New England Research Institutes, Watertown, MA, USA) using SAS software, version 9.1 (SAS Institute, Cary, NC, USA). Complete baseline data of 1049 of the 1050 randomized patients were analysed. There were six response variables: two symptom scores, three SF-36 scales and the Sexual Health Scale. The response variables were assessed at study months 0 (baseline), trial months 12, 24, 36, 48 and study month 54 (6 months post-trial). Repeated-measures analyses of covariance (ANCOVAS) were used to investigate changes in each of the six response variables over time controlling for baseline level of the variable, stratum (cirrhosis/noncirrhotic fibrosis), randomization assignment (treatment/control), time, age, gender and race as fixed effects. For any factors significantly associated with a response variable, we tested the interaction of that factor and time. The Conditional Model Concordance Correlation Coefficient was used for assessing the adequacy of each model;[46] the coefficient can range from −1 to 1 and a value ≤0 indicates poor fit.

To evaluate the association of clinical and histological outcomes with the response variables, we included a time varying covariate with two categories: whether or not patient met the definition of any outcome at or before the date of the visit at which the response variable was assessed. The patient's first outcome (including death) was used for analyses. The covariate was added to each model as a predictor after controlling for stratum (cirrhosis/noncirrhotic fibrosis), randomization assignment, time, age, gender, race and baseline level of the response variable. Patients lost to follow-up (including those who died) provided no information after the point they were lost. For analyses

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of histological progression (≥2-point increase in Ishak fibrosis score), we analysed only patients in the non-cirrhotic fibrosis stratum with at least one follow-up biopsy. For the Sexual Health Scale, separate analyses were performed for male and female subjects.

RESULTS

Characteristics of cohort

A flowchart of participants enrolled in the HALT-C Trial and the 1049 with complete baseline data included in these analyses is shown in Figure 1. At entry, the mean age of the participants was 50.1 ± 7.2 years, 71% were men and 72% were non-Hispanic Whites (Table 1). One-third of participants (34%) were taking antidepressant or anxiolytic medications at baseline. Although most participants had previously used alcohol (83%) or smoked cigarettes (76%), few were still drinking (17%) or smoking (30%) at baseline. At baseline, 622 participants (59%) had noncirrhotic fibrosis (Ishak 3–4) and 427 (41%) had cirrhosis (Ishak 5–6). The mean body mass index was higher and HCV RNA levels were lower in participants with cirrhosis than in those with fibrosis, while the other clinical and demographic features were similar in the fibrosis and cirrhosis groups. No major differences were present at baseline between the treatment and control groups (data not shown).

Changes in symptoms and scores over time

Table 2 shows the slope coefficients derived from the final ANCOVA models for the association of each

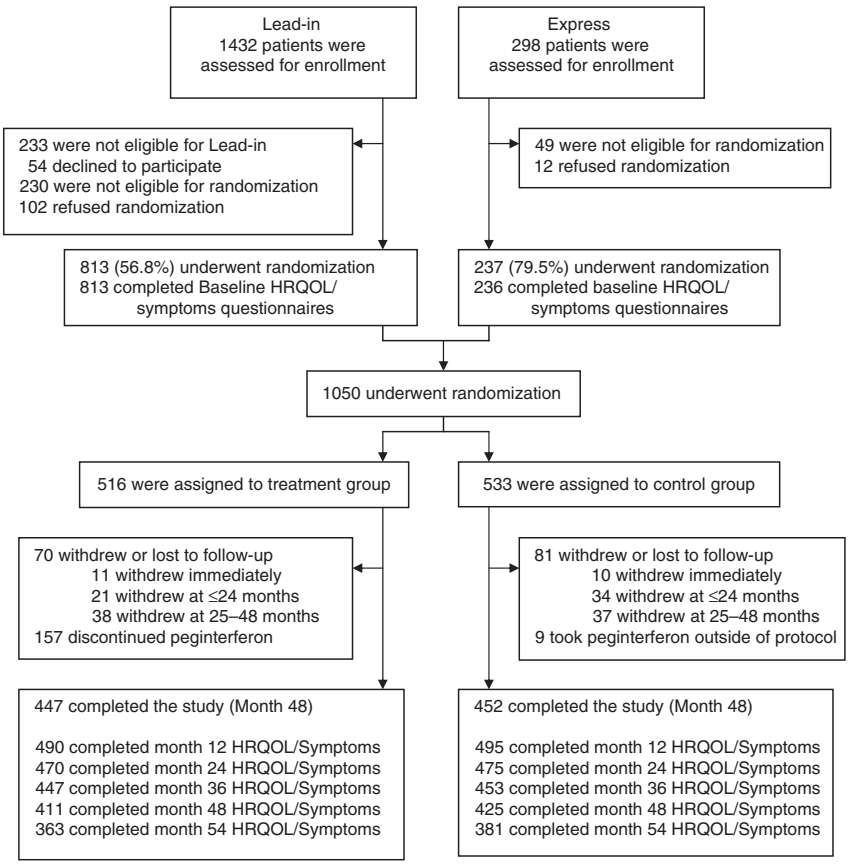

Figure 1. Enrolment, randomization, and follow-up of study participants. Patients were enrolled in either the lead-in cohort of patients who underwent another course of antiviral treatment with peginterferon and ribavirin within the study or in the express cohort of patients who were initially treated outside the study. They were then randomly assigned to either the treatment or the control group and were followed up for clinical outcomes and histological evidence of progression of liver disease.

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Table 1. Selected demographic and historical features of participants

	All patients (n = 1049), % or mean ± s.d.	Patients with noncirrhotic fibrosis at baseline (n = 622), % or mean ± s.d.	Patients with cirrhosis at baseline (n = 427), % or mean ± s.d.	P-value*
Demographics				
Age (years)	50.1 ± 7.2	50.1 ± 7.3	50.1 ± 7.0	0.99
Gender (% female)	29	29	28	0.60
Marital status (% married or living as married)	55	57	53	0.20
Education level (% college graduate)	21	22	19	0.33
Race/ethnicity (% White, non-Hispanic)	72	72	71	0.81
Body Mass Index (kg/m^2)	29.9 ± 5.5	29.5 ± 5.6	30.3 ± 5.3	0.03
Medical disorders				
History of diabetes mellitus (% of patients)	17	16	20	0.08
History of serious or other heart disease (% of patients)	13	13	13	0.97
History of major depression (% of patients)	7	7	7	0.57
Anxiolytic/antidepressant use at baseline (% of patients)	34	34	35	0.76
Hepatitis factors				
HCV genotype 1 (% of patients)	94	94	93	0.34
HCV RNA level at baseline ($\log_{10}$ of IU/mL)	6.4 ± 0.5	6.5 ± 0.5	6.3 ± 0.6	<0.001
Smoking and alcohol use				
Ever drank alcohol regularly (% of patients)	83	83	84	0.63
Lifetime alcohol consumption (number of drinks)	18 159 ± 30 881	17 339 ± 30 536	19 359 ± 31 378	0.30
Regular alcohol user at baseline (% of patients)	17	19	14	0.08
Ever smoked cigarettes (% of patients)	76	75	78	0.24
Current smoker at baseline (% of patients)	30	29	31	0.56
Baseline HRQOL and symptom scores†				
SF-36 Vitality Subscale score	54.2 ± 23.0	55.4 ± 22.3	52.5 ± 23.9	0.05
SF-36 Physical Summary score	44.5 ± 11.3	45.3 ± 11.1	43.4 ± 11.5	0.009
SF-36 Mental Summary score	50.5 ± 9.0	51.1 ± 8.3	49.5 ± 9.9	0.005
Sexual Health score (men only)	74.3 ± 28.4	76.5 ± 27.2	71.2 ± 29.7	0.01
Sexual Health score (women only)	62.9 ± 35.4	64.0 ± 35.8	61.3 ± 34.8	0.53
Fatigue	3.4 ± 2.7	3.3 ± 2.6	3.5 ± 2.8	0.11
General Well-Being	2.7 ± 2.2	2.6 ± 2.2	2.9 ± 2.3	0.13

* P-value for a t-test or chi-squared comparison of participants with baseline noncirrhotic fibrosis vs. participants with baseline cirrhosis.
† SF-36 and Sexual Health scores have a 100-point scale (0 = worst; 100 = best); Fatigue scores have a 10-point scale (none = 0 to worst ever = 10); and General Well-Being scores have a 10-point scale (very good = 0 to very bad = 10).

patient characteristic with the six response variables (symptoms, SF-36 and Sexual Health scores). None of the interaction effects of patient characteristics by time was statistically significant. Thus, each slope coefficient estimates the difference in the response variable at each value of the patient characteristic averaged over the entire time period. For categorical predictors (such as gender), the coefficient represents the difference between the average level of response variable in two groups. For continuous predictors (such as age), the coefficient represents the relationship of the average level of response variable to the average level of predictor. The Conditional Model Concordance Correlation Coefficient was consistent with adequate to good fit of each model. At month 12, 21 participants had experienced a clinical outcome (2 in the fibrosis stratum and 19 in the cirrhosis stratum). At month 54, 85 participants had experienced a clinical outcome (28 in the fibrosis stratum and 57 in the cirrhosis stratum).

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Table 2. Results of repeated-measures analysis of covariance of symptoms, HRQOL and Sexual Health scores

	Fatigue* (n = 1047)	General Well-Being† (n = 1040)	SF-36 Physical Summary score† (n = 1044)	SF-36 Mental Summary score† (n = 1044)	SF-36 Vitality Subscale score† (n = 1048)	Sexual Health score† (n = 742 males)	Sexual Health score† (n = 292 females)
Age (+1 year)	−0.001 (0.88)	0.007 (0.31)	−0.03 (0.43)	0.07 (0.04)	0.05‡ (0.46)	−0.33 (0.01)	0.20 (0.22)
Gender (male vs. female)	−0.58 (<0.001)	0.36§ (0.002)	1.65 (0.002)	1.27 (0.01)	4.26 (<0.001)	NA	NA
Race (White, non-Hispanic vs. other)	0.35 (0.009)	−0.23 (0.03)	0.55 (0.27)	−0.82 (0.10)	−3.30 (0.002)	−0.30 (0.87)	2.90 (0.33)
Stratum (noncirrhotic fibrosis vs. cirrhosis)	−0.41 (0.009)	0.21 (0.04)	1.04 (0.02)	0.57 (0.22)	3.38 (<0.001)	1.45 (0.36)	4.81 (0.11)
Randomization group (treatment vs. control)	0.13 (0.28)	−0.07 (0.48)	−0.84 (0.06)	−0.45 (0.32)	−2.88 (0.002)	−8.70 (<0.001)	−2.73 (0.35)
Clinical outcome (had outcome before visit vs. no outcome or had outcome after visit)	0.60 (<0.001)	−0.52 (<0.001)	−4.61 (<0.001)	−1.22 (0.03)	−3.92 (<0.001)	−11.21 (<0.001)	−4.13 (0.24)
Time (M12, M24, M36, M48, M54)¶	(0.93)	(0.002)	(0.006)	(0.11)	(0.71)	(0.07)	(0.09)
Conditional Model Concordance Correlation Coefficient**	0.41	0.45	0.63	0.35	0.54	0.46	0.40

Slope coefficients (and *P*-values) for each patient characteristic in relation to each response, controlling for all other covariates are provided.
NA, not applicable.
* Higher score indicates more fatigue.
† Higher score indicates better well-being, health-related quality of life (HRQOL) or sexual health.
‡ For continuous predictors, the coefficient represents the relationship of the average level of response variable to the average level of predictor. For the SF-36 Vitality Subscale score, the coefficient for age =0.05 indicates that an increase of 1 year in age was associated with an estimated increase of 0.05 units in the mean of the Vitality score.
§ For categorical predictors, the coefficient represents the difference between the average levels of response variable in two groups. For the General Well-Being response variable, the coefficient for gender of 0.36 indicates that the average for males was 0.36 points higher than the average for females.
¶ Test of equality of all five time points.
** Conditional Model Concordance Correlation Coefficient was used for assessing the adequacy of each model.

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Symptoms

At baseline, self-reported Fatigue and General Well-Being scores were not significantly different in participants with fibrosis compared with those with cirrhosis (Table 1). General Well-Being fluctuated significantly over time ($P = 0.002$), but, on average, participants with fibrosis reported greater General Well-Being (0.21 units, $P = 0.04$) than those with cirrhosis (Figure 2a). Although Fatigue did not change significantly over time ($P = 0.93$), participants with fibrosis reported less Fatigue on average (−0.41 units, $P = 0.009$) than those with cirrhosis (Figure 2b). Furthermore, participants in whom a clinical outcome developed reported significantly lower General Well-Being (−0.52 units, $P < 0.001$) and greater Fatigue (0.60 units, $P < 0.001$) compared with patients who did not develop an outcome. Assignment to the treatment or control group was not significantly associated with either Fatigue or General Well-Being scores over time (Figure 2c).

SF-36 scores

At baseline, participants in the cirrhosis stratum had significantly lower scores on the SF-36 Physical Summary, Mental Summary and Vitality scales compared with those in the fibrosis stratum (Table 1). Only the Physical Summary scores changed significantly over the course of the study ($P = 0.006$). On average, participants with fibrosis reported higher Physical Summary scores than those with cirrhosis (1.04 points, $P = 0.02$), but scores in both groups declined over time (Figure 3a). Furthermore, the decline in Physical Summary scores was greater for persons who experienced a clinical outcome than for those who did not (−4.61 points, $P < 0.001$). As shown in Figure 3b, participants with a clinical outcome also had a greater decline in the Mental Summary scores (−1.22 points, $P = 0.03$) compared with patients without an outcome. Histological stratum was not significantly associated with Mental Summary scores. Participants who experienced a clinical outcome had a significantly greater decline in Vitality scores than those who did not (−3.92 points, $P < 0.001$, Figure 3c). In addition, participants in the fibrosis stratum had higher Vitality scores than participants in the cirrhosis stratum (3.38 points, $P < 0.001$).

Vitality scores (Figure 3d) were significantly lower in participants assigned to the treatment group compared with control participants (−2.88 points, $P = 0.002$); after therapy was stopped at month 48, Vitality scores rebounded to baseline levels and to the level in the control group. Also, we detected a trend towards lower Physical Summary scores in the treatment group compared with the control group (−0.84 points, $P = 0.06$); however, treatment/control assignment was not significantly associated with Mental Summary scores (Figure 3e).

Sexual health scores

Figure S1 provides information on the changes from baseline to 3.5 years by gender and treatment group in sexual enjoyment, desire and function questions (Appendix A). In general, approximately half of patients reported no change over the course of the study. Compared with control patients, a greater percentage of treated patients reported a decline over time in sexual enjoyment (Figure S1a: 35% vs. 24% for men and 32% vs. 25% for women); sexual desire (Figure S1b: 33% vs. 23% for men and 26% vs. 22% for women); and sexual function (Figure S1c: 37% vs. 25% for men and 33% vs. 20% for women). Likewise, treated patients were also less likely to report an improvement over time in enjoyment, desire and function compared with control patients.

At baseline, men in the cirrhosis stratum had significantly lower scores on the composite Sexual Health Scale compared with men in the fibrosis stratum, while scores were not significantly different for women (Table 1). The Sexual Health scores declined slightly, but the change over time was not statistically significant (Table 2). Histological stratum was not significantly associated with Sexual Health scores in the ANCOVA model. As shown in Figure 4a, men who experienced a clinical outcome had lower scores on average than those without outcomes (−11.21 points, $P < 0.001$). Among men (Figure 4b), lower Sexual Health scores were seen in the treatment group compared with the control group (−8.70 points, $P < 0.001$). The majority of the decline in the treated men occurred early, with a minimal decline thereafter that paralleled the decline in the control group (P for trend = 0.07). In contrast, women had little change in mean Sexual Health scores over time and no significant difference was observed between treated and control female participants.

Association between histological progression and changes in HRQOL and symptoms

Among the 476 participants in the noncirrhotic fibrosis stratum with at least one follow-up liver biopsy,

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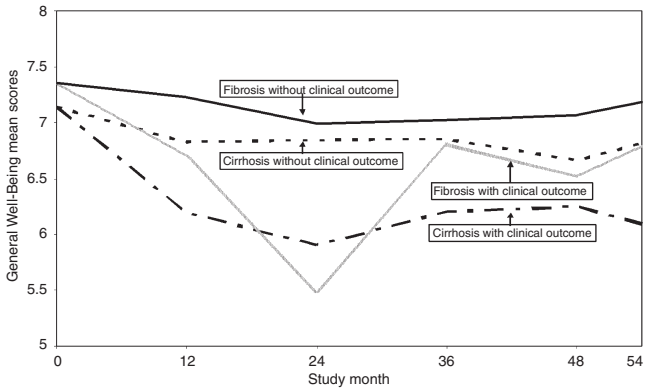
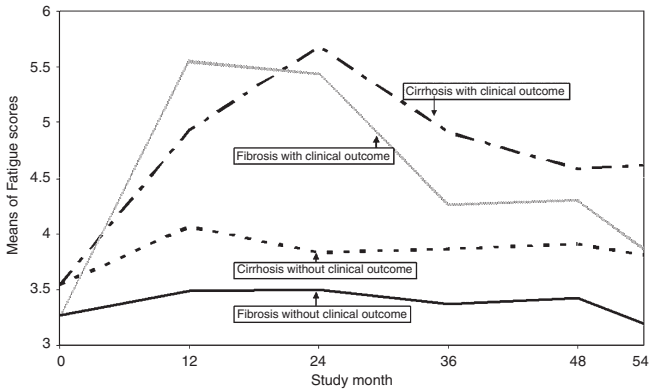
(a)



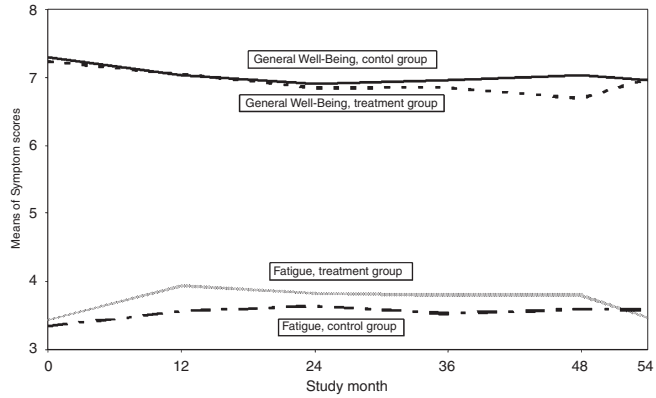
Number at risk						
Fibrosis without clinical outcome	620	566	532	496	480	423
Cirrhosis without clinical outcome	420	381	342	289	261	231
Fibrosis with clinical outcome	0	2	8	20	26	29
Cirrhosis with clinical outcome	0	19	36	56	58	56

(b)



Number at risk						
Fibrosis without clinical outcome	622	570	538	501	484	427
Cirrhosis without clinical outcome	425	383	344	295	263	231
Fibrosis with clinical outcome	0	2	8	20	26	29
Cirrhosis with clinical outcome	0	19	37	57	60	57

(c)



Number at risk						
General Well-Being control group	528	487	460	430	418	378
General Well-Being treatment group	512	481	458	431	407	361
Fatigue treatment group	517	485	461	441	411	363
Fatigue control group	530	489	466	432	422	381

Figure 2. Means of (a) General Well-Being and (b) Fatigue scores over time by clinical outcome and stratum; (c) Symptoms by treatment assignment. General Well-Being scores ranged from 0 (very good) to 10 (very bad). Fatigue scores ranged from 0 (none) to 10 (worst ever).

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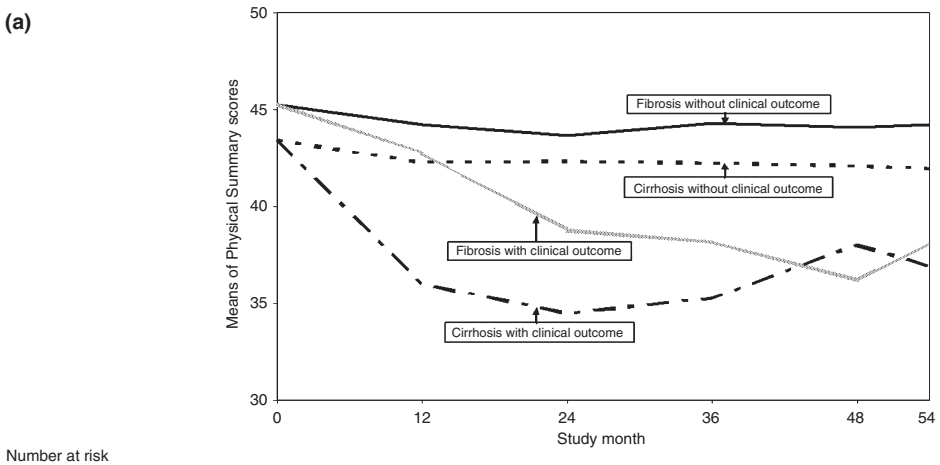
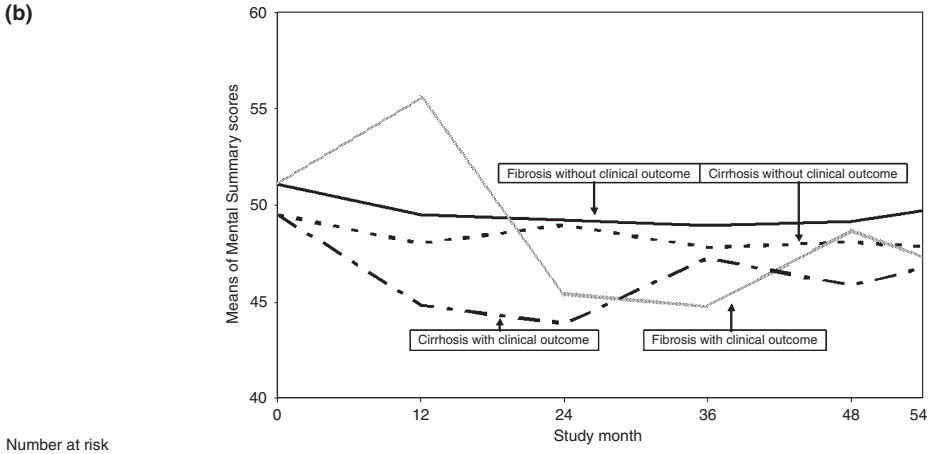


Number at risk

Fibrosis without clinical outcome	618	571	542	507	477	420
Cirrhosis without clinical outcome	426	380	344	297	260	229
Fibrosis with clinical outcome	0	2	8	22	26	28
Cirrhosis with clinical outcome	0	19	38	59	59	57



Number at risk

Fibrosis without clinical outcome	618	571	542	507	477	420
Cirrhosis without clinical outcome	426	380	344	297	260	229
Fibrosis with clinical outcome	0	2	8	22	26	28
Cirrhosis with clinical outcome	0	19	38	59	59	57

Figure 3. Means of (a) SF-36 Physical Summary, (b) Mental Summary and (c) Vitality scores over time by clinical outcome and stratum; (d) SF-36 Vitality scores and (e) Summary Scores by treatment assignment. SF-36 scores range from 0 (worst score) to 100 (best score).

152 (32%) had an increase in Ishak score of ≥2 points during the study. In multivariate analyses, progression to cirrhosis was associated with a decrease in Vitality scores (−2.21 points, $P = 0.04$), an increase in Fatigue scores (0.44 units, $P = 0.001$) and worsening of General Well-Being scores (−0.31 units, $P = 0.003$) during follow-up. In contrast, Physical and Mental Summary scores and Sexual Health scores did not change significantly in association with worsening of fibrosis.

DISCUSSION

In persons with early stages of CHC, symptoms tend to be mild, and HRQOL is relatively well preserved. However, these clinical features are often worse in patients with advanced cirrhosis assessed in cross-sectional studies. The number of patients with liver disease progression serially assessed over time has been limited. In the current analyses from a large prospective randomized controlled trial of long-term low-dose

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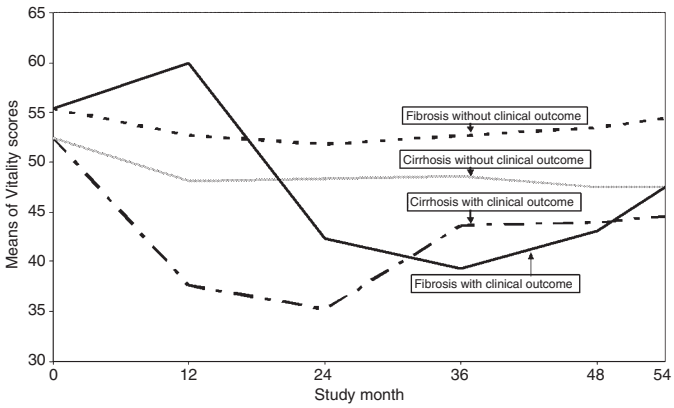
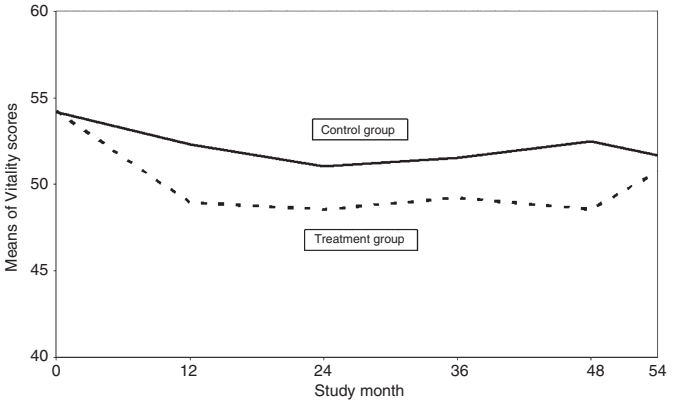
(c)



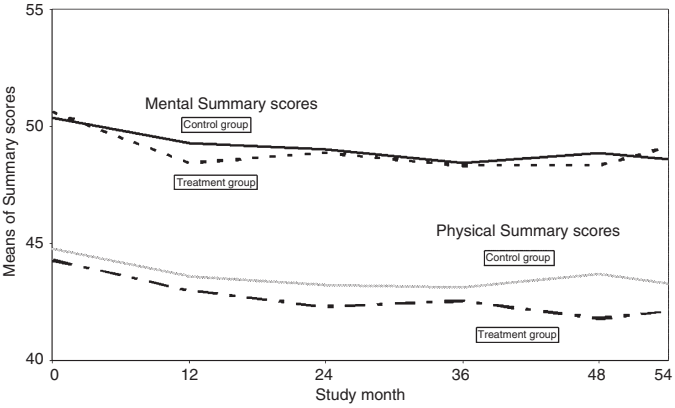
Number at risk						
Fibrosis without clinical outcome	621	575	547	509	479	421
Cirrhosis without clinical outcome	427	383	347	298	261	229
Fibrosis with clinical outcome	0	2	8	22	26	28
Cirrhosis with clinical outcome	0	19	38	59	61	57

(d)



Number at risk						
Control group	532	492	471	445	416	378
Treatment group	516	487	469	443	411	357

(e)



Number at risk						
Mental Summary control group	529	488	470	443	413	377
Mental Summary treatment group	515	484	462	442	409	357
Physical Summary control group	529	488	470	443	413	377
Physical Summary treatment group	515	484	462	442	409	357

Figure 3. (*Continued*)

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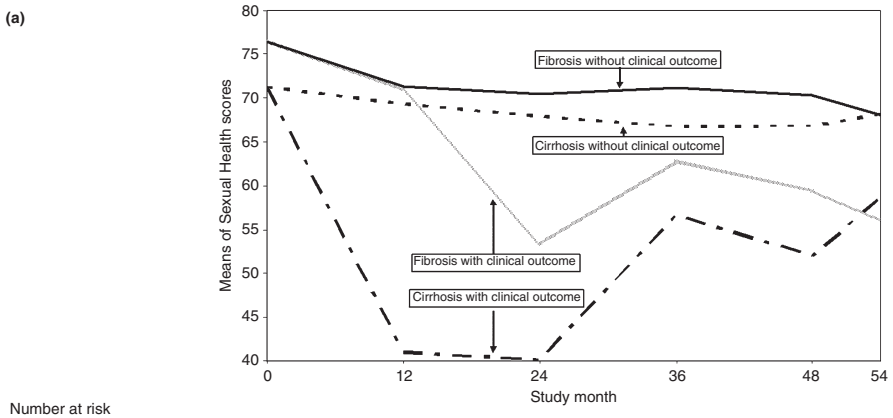
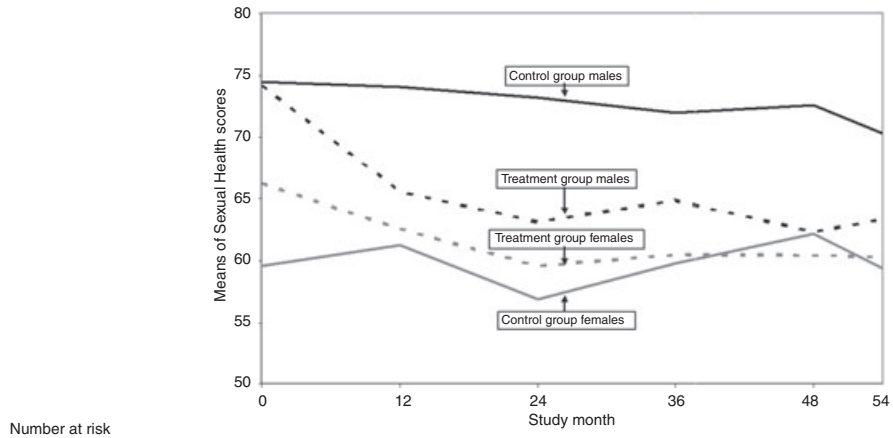


Number at risk						
Fibrosis without clinical outcome	436	401	380	353	339	303
Cirrhosis without clinical outcome	306	274	257	220	195	164
Fibrosis with clinical outcome	0	2	5	13	16	21
Cirrhosis with clinical outcome	0	13	25	40	38	41



Number at risk						
Control group males	383	351	338	321	305	273
Treatment group males	359	339	329	305	283	256
Treatment group females	147	139	137	127	116	97
Control group females	145	137	126	121	110	96

Figure 4. Means of (a) Sexual Health scores in males by clinical outcome and stratum, (b) Sexual Summary scores by treatment group and gender over time. Sexual Health scores range from 0 (worst score) to 100 (best score).

peginterferon therapy for advanced-stage CHC, HRQOL was prospectively assessed. Clinical progression of liver disease was associated with statistically and clinically significant declines in all components of HRQOL. Symptoms of fatigue were also greater and general well-being was lower in participants with cirrhosis and participants who experienced a clinical endpoint. Similarly, Physical Summary and Vitality scores were lower in participants with cirrhosis than in those with noncirrhotic fibrosis. These findings, while not unexpected, provide evidence that the selected instruments (i.e., the SF-36 and visual analogue symptom scales) can reliably correlate with important baseline clinical features of CHC as well as an objective measure of worsening of disease severity over time.

The current results also demonstrate that maintenance peginterferon therapy was associated with statistically and clinically significant decreases in Vitality and Physical Summary scores. Furthermore, men who received peginterferon reported significant declines in sexual health that did not rebound after cessation of treatment, despite minimal worsening of fatigue and well-being. Mental Summary scores, however, did not worsen significantly with peginterferon therapy. Our findings suggest that poor baseline mental health scores among participants with CHC may relate more

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to underlying medical and psychiatric comorbidities and less to severity of liver disease, whereas the physical domains of HRQOL assessment reflect disease severity and progression more reliably. This inference is supported by the high frequency of anxiolytic/antidepressant medication use as well as the frequent history of prior alcohol and drug use disorders in the HALT-C patient population.[47] In addition, the low dose of peginterferon used (without ribavirin) and dose reductions to maintain treatment tolerability may have yielded a peginterferon dose that was too low to cause worsening in mental health scores over time.

Maintenance peginterferon therapy for nonresponder patients with advanced CHC was not only ineffective in decreasing disease progression and preventing clinical outcomes,[38] but also impaired HRQOL and sexual health (the latter observed only among men). A similar decline in symptoms of fatigue and well-being that distinguished treated patients from untreated control patients was not identified. Our observation of a treatment-related reduction in HRQOL and sexual health but not of symptoms suggests that the clinical instrument used to assess symptoms was less sensitive than the SF-36 instrument used to measure HRQOL. Alternatively, the less pronounced effects of therapy on symptoms may have resulted from the fact that peginterferon doses could be reduced because of severe fatigue and other drug side effects, which could have blunted the intensity and duration of treatment-related symptoms. Similarly, symptom scores did not improve significantly after month 48, when patients still taking low-dose peginterferon stopped treatment per protocol.

Previous studies have shown that HRQOL is poor among patients with CHC compared with uninfected population controls and is substantially impaired in patients with histologically documented cirrhosis.[5, 6, 8–10, 12, 13] A recent prospective study demonstrated that higher HRQOL predicted lower mortality in patients with cirrhosis awaiting liver transplantation.[48] The current prospective study supports the previous studies, demonstrating that HRQOL declines when cirrhosis develops and declines further when disease complications and decompensation occur in patients with cirrhosis. Mean SF-36 scores were consistently lower in HALT-C patients than scores for age-matched general US population norms.[43, 44] Thus, our findings support use of changes in HRQOL as a variable of interest in subsequent clinical trials of maintenance therapies for CHC. In previous analyses of the lead-in phase of HALT-C, HRQOL worsened significantly during full-dose peginterferon and ribavirin therapy and improved back to baseline levels when treatment was stopped. Furthermore, patients with an SVR had improvements in HRQOL to levels that exceeded their baseline.[22] The results of the current analyses support the importance of changes in HRQOL as a potential surrogate marker for liver disease progression in patients with CHC followed up over several years.

The shortcomings of the current analyses include the limited range of disease severity among the HALT-C cohort, in that all enrolled participants had advanced fibrosis and did not have a response to previous antiviral treatment. No participants with early or intermediate stages of disease and no treatment naïve patients were included to assess whether HRQOL or symptoms worsen over time with or without peginterferon therapy. Still, in participants who had noncirrhotic fibrosis at the start of therapy and who did not progress to cirrhosis histologically, symptoms and HRQOL were stable, suggesting that these instruments are reliable markers for disease progression or its absence in late stages of CHC. Another shortcoming of the current study was the use of a sexual health assessment instrument that had not been validated in other studies or the general population. The Sexual Health Scale used in this trial was calculated from three questions regarding sexual enjoyment, desire and function. Men reported lower Sexual Health Scale scores while receiving maintenance peginterferon therapy. However, the scale will need validation before it can be used widely for the sexual health. The gender differences in sexual health components noted in the current analyses are consistent with previous studies.[36] However, the greater impact of treatment and disease progression on Sexual Health scores in men could be attributable to differing side-effect profiles of peginterferon or hormonal changes with liver disease progression in men compared with women. Changes in usage of antihypertensive or antidepressant medications over time were not included in the analyses and could have been potential confounders.

In summary, our study findings indicate that the physical components of HRQOL and sexual health (in men) decline during low-dose, long-term peginterferon therapy. In addition, clinical progression of disease is associated with lower SF-36 Physical and Mental Summary scores and worsening of Fatigue and General Well-Being over 54 months of follow-up. These results help validate the utility of the selected instruments in detecting clinically significant symptoms and changes in HRQOL over time in patients with

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chronic liver disease and provide support for their use as a tool for monitoring disease progression in future longitudinal studies of CHC.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Changes over time by gender and treatment group in sexual enjoyment, desire and function components of the Sexual Health Scale.

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APPENDIX A

Symptoms form

Mark each line with an "x" that best describes how you have felt during the past week. Place an "x" on each line below .

	None	Worst ever
a. Fatigue		
b. Nausea		
c. Pain over the liver area		
d. Poor appetite		
e. Headaches		
f. Muscle/joint aches or pains		
g. Itchiness		
h. Irritability		
i. Depression/Sadness		

Mark with an "x" the place on the line below that best indicates how you feel overall .

Very Good — Very Bad

Sexual Health Scale items

Mean score on the following three questions if answered 1–5 (transformed to a 0–100 scale):

How much of the time during the last four weeks, have you …

- **Felt your health interfered with your enjoyment of sex?**
- **Lacked interest in sex?**
- **Felt your health interfered with your sexual performance?**

Answer possibilities:

Not at all	A little bit	Moderately	Quite a bit	Extremely	Does not apply
1	2	3	4	5	−1

APPENDIX B

University of Massachusetts Medical Center, Worcester, MA: (Contract N01-DK-9-2326) Gyongyi Szabo, MD, Barbara F. Banner, MD, Maureen Cormier, RN, Donna Giansiracusa, RN.

University of Connecticut Health Center, Farmington, CT: (Grant M01RR-06192) Gloria Borders, RN, Michelle Kelley, RN, ANP.

Saint Louis University School of Medicine, St Louis, MO: (Contract N01-DK-9-2324) Bruce Bacon, MD, Brent Neuschwander-Tetri, MD, Elizabeth M. Brunt, MD, Debra King, RN.

Massachusetts General Hospital, Boston, MA: (Contract N01-DK-9-2319, Grant M01RR-01066; Grant 1 UL1 RR025758-01, Harvard Clinical and Translational Science Center) Raymond T. Chung, MD, Andrea E. Reid, MD, Atul K. Bhan, MD, Wallis A. Molchen, Cara C. Gooch.

University of Colorado School of Medicine, Denver, CO: (Contract N01-DK-9-2327, Grant M01RR-00051, Grant 1 UL1 RR 025780-01) Gregory T. Everson, MD, S. Russell Nash, MD, Jennifer DeSanto, RN, Carol McKinley, RN.

University of California – Irvine, Irvine, CA: (Contract N01-DK-9-2320, Grant M01RR-00827) John C. Hoefs, MD, John R. Craig, MD, M. Mazen Jamal, MD, MPH, Muhammad Sheikh, MD, Choon Park, RN.

University of Texas Southwestern Medical Center, Dallas, TX: (Contract N01-DK-9-2321, Grant M01RR-00633, Grant 1 UL1 RR024982-01, North and Central Texas Clinical and Translational Science Initiative) William M. Lee, MD, Thomas E. Rogers, MD, Peter F. Malet, MD, Janel Shelton, Nicole Crowder, LVN, Rivka Elbein, RN, BSN, Nancy Liston, MPH.

University of Southern California, Los Angeles, CA: (Contract N01-DK-9-2325, Grant M01RR-00043) Karen L. Lindsay, MD, MMM, Sugantha Govindarajan, MD, Carol B. Jones, RN, Susan L. Milstein, RN.

University of Michigan Medical Center, Ann Arbor, MI: (Contract N01-DK-9-2323, Grant M01RR-00042, Grant 1 UL1 RR024986, Michigan Center for Clinical and Health Research) Anna S. Lok, MD, Joel K. Greenson, MD, Pamela A. Richtmyer, LPN, CCRC, R. Tess Bonham, BS.

Virginia Commonwealth University Health System, Richmond, VA: (Contract N01-DK-9-2322, Grant M01RR-00065) Mitchell L. Shiffman, MD, Melissa J. Contos, MD, A. Scott Mills, MD, Charlotte Hofmann, RN, Paula Smith, RN.

Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD: T. Jake Liang, MD, David Kleiner, MD, PhD, Yoon Park, RN, Elenita Rivera, RN, Vanessa Haynes-Williams, RN.

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National Institute of Diabetes and Digestive and Kidney Diseases, Division of Digestive Diseases and Nutrition, Bethesda, MD: Jay H. Hoofnagle, MD, James E. Everhart, MD, Leonard B. Seeff, MD, Patricia R. Robuck, PhD, Elizabeth C. Wright, PhD.

University of Washington, Seattle, WA: (Contract N01-DK-9-2318) Chihiro Morishima, MD, David R. Gretch, MD, PhD, Minjun Chung Apodaca, BS, ASCP, Rohit Shankar, BC, ASCP, Natalia Antonov, M. Ed.

New England Research Institutes, Watertown, MA: (Contract N01-DK-9-2328) Anne M. Stoddard, ScD, Teresa M. Curto, MSW, MPH, Margaret C. Bell, MS, MPH, Raymond C. Rosen, PhD.

Armed Forces Institute of Pathology, Washington, DC: Zachary D. Goodman, MD.

Data and Safety Monitoring Board Members: (Chair) Gary L. Davis, MD, Guadalupe Garcia-Tsao, MD, Michael Kutner, PhD, Stanley M. Lemon, MD, Robert P. Perrillo, MD.

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