Integrated Care Increases Treatment and Improves Outcomes of Patients With Chronic Hepatitis C Virus Infection and Psychiatric Illness or Substance Abuse

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BACKGROUND & AIMS: **Patients with hepatitis C virus (HCV) infection with psychiatric disorders and/or substance abuse face significant barriers to antiviral treatment. New strategies are needed to improve treatment rates and outcomes. We investigated whether an integrated care (IC) protocol, which includes multidisciplinary care coordination and patient case management, could increase the proportion of patients with chronic HCV infection who receive antiviral treatment (a combination of interferon-based and direct-acting antiviral agents) and achieve a sustained virologic response (SVR).**

METHODS: **We performed a prospective randomized trial at 3 medical centers in the United States. Participants (n = 363 patients attending HCV clinics) had been screened and tested positive for depression, post-traumatic stress disorder, and/or substance use; they were assigned randomly to groups that received IC or usual care (controls) from March 2009 through February 2011. A midlevel mental health practitioner was placed at each HCV clinic to provide IC with brief mental health interventions and case management, according to formal protocol. The primary end point was SVR.**

RESULTS: **Of the study participants, 63% were non-white, 51% were homeless in the past 5 years, 64% had psychiatric illness, 65% were substance abusers within 1 year before enrollment, 57% were at risk for post-traumatic stress disorder, 71% had active depression, 80% were infected with HCV genotype 1, and 23% had advanced fibrosis. Over a mean follow-up period of 28 months, a greater proportion of patients in the IC group began receiving antiviral therapy (31.9% vs 18.8% for controls; $P = .005$) and achieved a SVR (15.9% vs 7.7% of controls; odds ratio, 2.26; 95% confidence interval, 1.15−4.44; $P = .018$). There were no differences in serious adverse events between groups.**

CONCLUSIONS: **Integrated care increases the proportion of patients with HCV infection and psychiatric illness and/or substance abuse who begin antiviral therapy and achieve SVRs, without serious adverse events. ClinicalTrials.gov # NCT00722423.**

Keywords: Care Integration; Hepatitis C; Substance Use Disorders; PTSD.

Abbreviations used in this paper: DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IC, integrated care; MHP, mental health provider; OR, odds ratio; SUD, substance use disorder; SVR, sustained virologic response; UC, usual care; VA, Veterans Affairs.

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See editorial on page 2015.

Approximately 1.8% of the US population has chronic hepatitis C. The current estimated prevalence of hepatitis C virus (HCV) infection among Veterans Affairs (VA) patients is 8.4%, and the prevalence in the 1945 to 1965 birth cohort is 13.5%.[1] Antiviral treatment has been shown to eradicate HCV, resulting in reduced complications and mortality from liver disease.[2–4] Numerous studies have indicated that HCV antiviral treatment is cost effective, even with new direct-acting antiviral (DAA) medications, for all but a few subsets of HCV patients.[5–7] Despite these data, to date, only a minority of HCV patients have received antiviral treatment. Cumulative data from the VA HCV Registry indicate that the percentage of VA patients with HCV who have ever received HCV antiviral therapy increased from 10.9% in 2004 to 14.4% in 2007 and to 23% in 2013.[8] In the general US population, an estimated 7% to 11% of HCV patients have had antiviral treatment.[9] Without an expansion in treatment rates, projections suggest an increasing HCV burden from the progression of cirrhosis and the development of hepatocellular carcinoma and liver failure.[10]

Within this past year, antiviral treatment of HCV has evolved from pegylated interferon and ribavirin, to pegylated interferon and ribavirin with DAAs, to interferon-free DAA combinations. This has been accompanied by greatly improved efficacy and reduced treatment-related side effects. Despite these improvements, a large percentage of HCV patients may be considered poor treatment candidates because of psychiatric comorbidity and/or substance use disorders (SUD). These comorbidities are common among HCV patients and have been the most frequently cited reasons for withholding antiviral therapy in the past.[9,11,12] Recent data from one VA medical center indicated that 45% of current HCV patients are poor candidates for interferon-free treatment based on active psychiatric/SUD comorbidity, and Medicaid currently precludes patients with active SUD from receiving interferon-free medications in many states.[13,14]

Integrated care (IC) refers to health care in which a variety of services are brought together to address interrelated health problems, and maximize patient compliance and outcomes. IC models have been effective in improving process measures and outcomes for treating psychiatric illness and substance use in primary care clinics and for improving treatment in acquired immune deficiency syndrome clinics.[15–17] To date, there is little information related to whether IC protocols can increase HCV treatment rates or viral outcomes.

Our objective was to determine if an IC protocol could increase sustained virologic response (SVR) and treatment rates among chronic HCV patients at risk for psychiatric and substance use comorbidities at 3 VA Medical Centers.

Materials and Methods

Design Overview

A detailed description of the study methods was published in 2013.[18] The study was conducted at 3 diverse VA medical centers with established HCV clinics staffed by experienced physicians (VA San Diego, VA Palo Alto, Bronx VA). Patients attending these HCV clinics were screened and recruited from March 2009 through February 2011 (Figure 1). Consented patients were randomized at each site 1:1 using random assignment software administered by the central site. The blocked, stratified, randomization sequence was concealed from research staff.

A data safety and monitoring board oversaw trial progress including enrollment, study outcomes, and serious adverse events. The study protocol is registered with ClinicalTrials.gov (#NCT00722423). The study was approved by the institutional review boards and each institution and all co-authors had access to the study data and reviewed and approved the final manuscript.

Study Participants

Study participants were VA patients with confirmed active HCV infection (HCV polymerase chain reaction positive) with substance use or psychiatric risk factors for antiviral treatment. All patients attending VA HCV clinics routinely received a standardized screening form as part of their clinical care, consisting of a Beck Depression Inventory, screening questionnaires for drug use, alcohol use (alcohol use disorders identification test), and posttraumatic stress disorder, as described previously[18] and as outlined in the Supplementary Materials and Methods section. Human immunodeficiency virus (HIV)/HCV coinfected patients were eligible at the Bronx site only to provide preliminary data on the benefits of the IC model for these patients. Exclusion criteria included non–HCV-related liver disease (except co-existing alcoholic liver disease), decompensated cirrhosis, or other significant life-threatening diseases (known malignancies and any incapacitating lung, cardiac, renal, or autoimmune medical disease). Ineligible patients also included treatment-experienced patients who were not considered re-treatment candidates (eg, previous treatment nonresponders or with significant adverse events). The definition of "homeless" refers to patients who were homeless by self-report within 5 years of the recruitment date; specific dates of being homeless without accessing available temporary services were not collected.

Intervention

Usual care. Patients randomized to usual care (UC) received the standard of care required for HCV patients consistent with current VA treatment guidelines. Each HCV

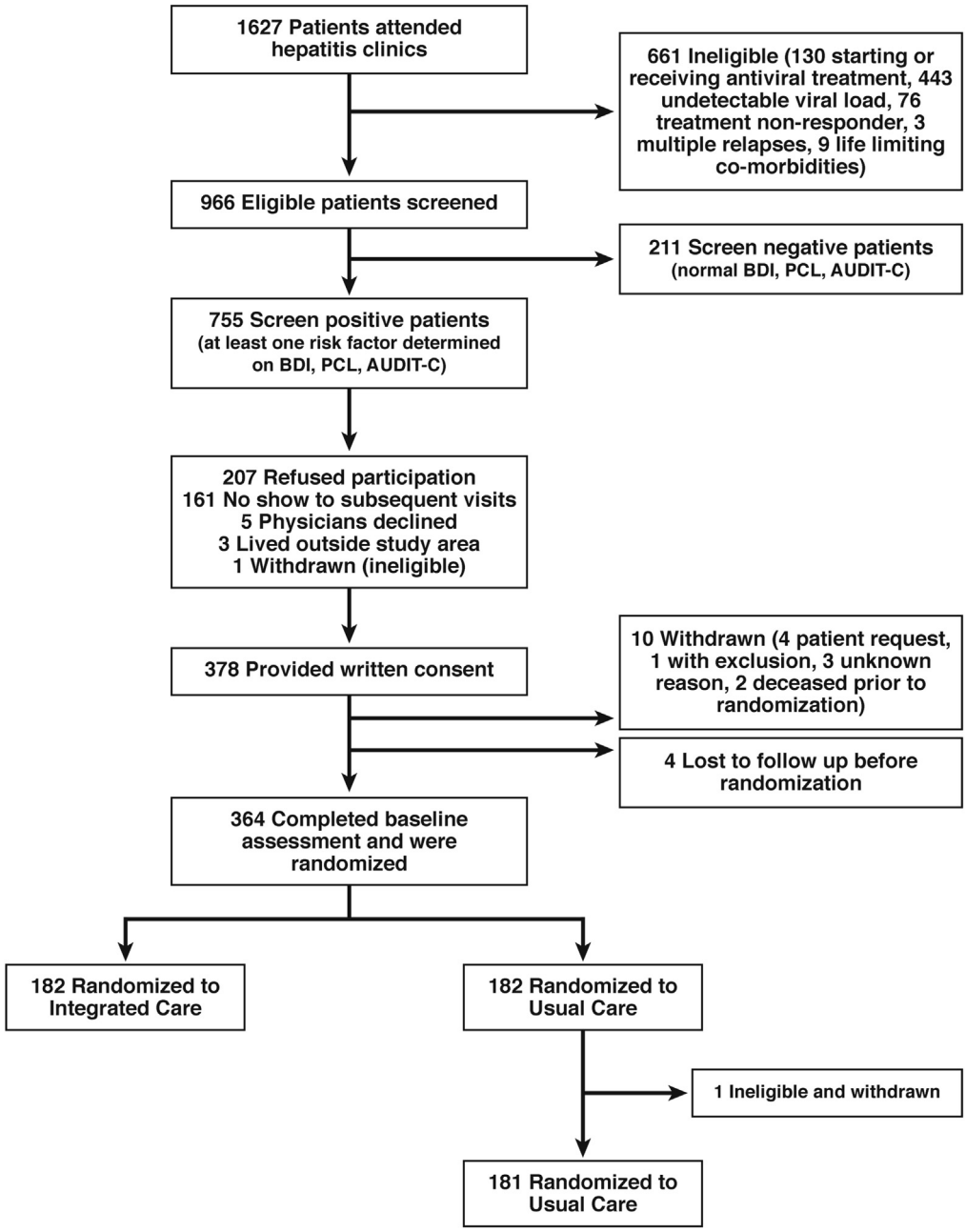

Figure 1. Patient enrollment and randomization. All HCV clinic patients were screened as part of standard clinical care. PCL, primary care PTSD screen checklist.

clinic had gastroenterology or infectious disease physicians working with clinical nursing or midlevel providers and a clinic psychiatrist or psychologist. Patients were either managed within the HCV clinic or referred to standard mental health and substance use clinics for further assessment and treatment as indicated by the severity of the risk factors. Mental health care provided by the HCV and non-HCV clinics did not follow a specific protocol and varied in accordance to the standard of care at those clinics.

Integrated care. The IC intervention was delivered according to a protocol manual by a midlevel mental health provider (MHP) located within each HCV clinic. The protocol included brief psychological interventions and case management provided in collaboration with clinic physicians, nurses, and other mental health providers. The MHP evaluated study participants and provided ongoing interventions designed to treat specific mental health problems. The MHP also facilitated a complete treatment evaluation, encouraged the initiation of antiviral treatment, and served as a regular contact and case manager. Further details of the IC case management protocol are available in the Supplementary Materials and Methods section and as described previously.[18]

Antiviral treatment. Physicians offered antiviral treatment to all patients in both study arms following recommendations and criteria in published professional organization and VA hepatitis C treatment guidelines.[19] These guidelines were applied at each site, and specified that patients should show stable psychiatric disease, compliance with treatment recommendations, and sobriety from substance use for a period of time as established in each clinic. Patients initiating antiviral

treatment were monitored using standard protocols. To promote inclusiveness and generalizability, the specific type of antiviral treatment was not specified in the study protocol, and was left to the discretion of the HCV clinical team. The standard of care for HCV treatment at study initiation was pegylated interferon alfa and ribavirin, but treatment was limited at all sites in late 2010 in anticipation of new therapies. DAA therapies, adding boceprevir or telaprevir to pegylated interferon alfa and ribavirin, were approved by the Food and Drug Administration and available in mid- to late 2011. Patients were monitored for significant adverse events that resulted in early termination of treatment.

Outcomes and Follow-Up Evaluation

The primary outcome for the study was SVR, determined by viral tests completed either 12 or 24 weeks after the termination of therapy, because either of these time frames currently are accepted as standard of care.[20,21] The main secondary outcomes were interferon-based treatment initiation and completion of prescribed treatment (range, 0%–100%). Treatment data were abstracted from medical records and included type and doses of medications initiated, planned treatment duration, and final treatment duration attained. Abstraction was conducted by trained research staff at each site, and then reviewed and audited by the data manager at the central site.

Other secondary outcomes included serious adverse events and health care utilization. Serious adverse events were defined as any hospitalization, emergency room visit, and/or death. All patients were followed up from treatment initiation through July 2012, at which time the intervention ended. Treatment completion outcomes were followed up through May 2013, and the primary outcome of SVR was followed up until August 2013.

Statistical Analysis

Sample size determination was performed as indicated in the Supplementary Materials and Methods section, and an enrollment of 360 patients was targeted to account for attrition. An intent-to-treat analysis was performed for all clinical outcomes. Descriptive statistics were used to summarize baseline characteristics. Univariate and multivariate analyses were used to assess the primary and secondary outcomes. See the Supplementary Materials and Methods section for further details of the statistical analysis.

Results

Study Participants

A total of 1627 patients attending 3 HCV clinics were evaluated; 966 patients were eligible for the study and screened for psychiatric and/or substance use risk factors as part of standard clinic care. Of these, 755 (78%) had a positive screen and 209 (22%) screened negative for risk factors. Of the screen-positive patients, 378 patients provided informed consent and 364 patients completed a baseline evaluation and were randomized (Figure 1). One patient was enrolled in error and withdrawn, leaving 182 patients in the IC arm and 181 patients in the UC arm. Patients were enrolled over 22 months, and the mean patient follow-up period across all sites was 28.1 months (SD, 5.53 mo).

The baseline characteristics for study participants are listed in Table 1, and were similar in the IC and UC groups. Participants were 63.5% non-white and had a high frequency of known barriers to access (88.7% were unemployed or disabled, 51.1% were homeless within the prior 5 years, 63.9% had a psychiatric illness, and 64.5% had active drug use within 1 year and/or active alcohol abuse based on a positive alcohol use disorders identification test-C score The mean Beck Depression Inventory score was 15.5, and 70.7% met the criteria for depression at enrollment. The UC group has a higher percentage of married and separated patients. There were no significant differences in any other baseline characteristic.

Sustained Viral Response

The number of patients with SVR was 2-fold greater in the IC group (29 patients; 15.9%) compared with the UC group (14 patients; 7.7%) and patients receiving IC were more likely to have an SVR (odds ratio [OR], 2.26; $P = .018$) in univariate analysis. The simple logistic regression between each baseline characteristic and SVR is shown in Table 2. The multivariate model showed that patients receiving IC were more likely to have an SVR than the UC group (OR, 2.26; $P = .022$) (Table 3). Primary genotype (OR, 2.20; $P = .033$ for genotypes 2, 3, 4 vs genotype 1), prior psychiatric disorder (OR, 0.44; $P = .017$ yes vs no), and active drug use (OR, 0.47; $P = .034$ for yes vs no) also were associated significantly with SVR. By adding site to the fitted model, the intervention effect stayed similar and site was not associated significantly with the SVR. Of the 42 patients with HIV/HCV co-infection, 6 patients (25%) initiated treatment and 3 patients (12.5%) achieved SVR in the IC arm, compared with 1 patient (5.6%) who initiated treatment and 0 patients with SVR in the UC arm ($P = .21$ and .25, respectively). An evaluation of the subgroups of patients with and without active drug and alcohol use at baseline is presented in the Supplementary Materials and Methods section.

Time to Treatment Initiation

Patients in the IC arm were more likely to initiate treatment over time (Figure 2*A*). The overall treatment initiation rate in the IC arm was 58 of 182 (31.9%) compared with 34 of 181 (18.8%) in the UC arm ($P =$

Table 1. Patient Characteristics

	Total (n = 363), n (%)	Integrated care (n = 182), n (%)	Usual care (n = 181), n (%)	*P* value
Demographics				
Mean age, *y* (SD)	55.4 (5.65)	55.3 (5.51)	55.5 (5.79)	.47
Mean BMI (SD)	27.7 (4.83)	27.5 (5.11)	27.8 (4.54)	.43
Sex				
Male	355 (97.8)	178 (97.8)	177 (97.8)	1.00
Female	8 (2.2)	4 (2.2)	4 (2.2)	
Race/ethnicity				
African American or black	141 (39.3)	66 (36.7)	75 (41.9)	.65
White (non-Hispanic)	131 (36.5)	69 (38.3)	62 (34.6)	
Hispanic	65 (18.1)	32 (17.8)	33 (18.4)	
Others	22 (6.1)	13 (7.2)	9 (5)	
Marital status				
Single	82 (22.8)	47 (26.1)	35 (19.4)	.045
Married	60 (16.7)	26 (14.4)	34 (18.9)	
Separated	47 (13.1)	16 (8.9)	31 (17.2)	
Divorced	153 (42.5)	79 (43.9)	74 (41.1)	
Widowed	18 (5)	12 (6.7)	6 (3.3)	
Education				
Grades 1–11	38 (10.5)	21 (11.5)	17 (9.4)	.81
High school/GED	119 (32.9)	56 (30.8)	63 (35)	
Some college	167 (46.1)	86 (47.3)	81 (45)	
College/postgraduate	38 (10.5)	19 (10.4)	19 (10.6)	
Employment				
Full and part time	41 (11.3)	21 (11.6)	20 (11)	.87
Unemployed	141 (39)	69 (38.1)	72 (39.8)	
Disabled	138 (38.1)	72 (39.8)	66 (36.5)	
Retired and others	42 (11.6)	19 (10.5)	23 (12.7)	
Homeless in past 5 years				
Positive	179 (51.1)	86 (48.9)	93 (53.4)	.40
Clinical characteristics				
Primary genotype				
Type 1	281 (79.6)	148 (83.1)	133 (76)	.11
Types 2, 3, and 4	72 (20.4)	30 (16.9)	42 (24)	
Prior liver biopsy	116 (32)	60 (33)	56 (30.9)	.74
Biopsy after randomization	104 (28.7)	59 (32.4)	45 (24.9)	.13
PTSD risk				
Positive	201 (57.6)	97 (56.1)	104 (59.1)	.59
HIV/HCV co-infection	42 (11.6)	24 (13.3)	18 (10)	.41
Prior HCV antiviral treatment	44 (12.1)	19 (10.4)	25 (13.8)	.34
Prior psychiatric illness	232 (63.9)	113 (62.1)	119 (65.7)	.51
Prior substance abuse	240 (66.1)	118 (64.8)	122 (67.4)	.66
Number of prior medical illness				
Mean (SD)	1.04 (1.06)	0.99 (1.01)	1.1 (1.11)	.36
Prior medical illness	237 (65.3)	115 (63.2)	122 (67.4)	.44
Screen AUDIT-C score				
Mean (SD)	2.27 (3.2)	2.09 (2.97)	2.46 (3.41)	.37
Screen AUDIT-C (≥4 as positive)[a]				
Positive	96 (27.1)	46 (26.1)	50 (28.1)	.72
Screen BDI score				
Mean (SD)	15.5 (9.82)	15.4 (10.1)	15.5 (9.57)	.65
Screen BDI (≥10 positive)[b]				
Positive	248 (70.7)	123 (71.1)	125 (70.2)	.91
Alcohol drinks at baseline month, n				
Mean (SD)	11.4 (33.7)	12.8 (36.4)	10.1 (30.8)	.95
Active drug use at baseline (within 1 year)[c]	172 (47.4)	81 (44.5)	91 (50.3)	.29
Fibrosis level				
Mean (SD)	2.26 (1.68)	2.3 (1.75)	2.22 (1.61)	.93

Table 1. Continued

	Total (n = 363), n (%)	Integrated care (n = 182), n (%)	Usual care (n = 181), n (%)	*P* value
Advanced fibrosis,[d] (%)	28/124 (22.6)	15/60 (25.0)	13/64 (20.3)	.67
Site				
San Diego, n	157	78	79	
Bronx, n	124	63	61	
Palo Alto, n	82	41	41	

AUDIT, alcohol use disorders identification test.; BDI, Beck Depression Inventory; PTSD, post-traumatic stress disorder.
[a]Screen alcohol use disorders identification test-C–positive score of 4 or higher at baseline. Patients with a positive alcohol use disorders identification test-C included 18% with a score of 4 to 7 and 9% with a score of 8 or higher.
[b]Screen BDI-positive score includes scores of 10 or higher. Overall this included 35% of patients with mild depression (scores, 10–18), 27% with moderate depression (scores, 19–29), and 9% with severe depression (score, >30).
[c]Self-report active drug use and/or positive urine toxicology within 1 year of baseline (not including marijuana use).
[d]Advanced fibrosis: Metavir fibrosis scores of 3 to 4 or Ishak fibrosis scores of 4, 5, and 6.

.0054). The log-rank test showed that the time to treatment initiation was significantly different between the IC and UC groups ($P = .003$) (Figure 2*B*).

The multivariate Cox regression model showed that patients treated with IC started treatment earlier than patients treated with UC (hazard ratio [HR], 2.01; $P = .002$), and the rate of starting treatment was increased by 101% for subjects treated with IC (Table 3). We also found that homelessness in the past 5 years (HR, 1.88; $P = .005$ for yes vs no), active drug use (HR, 0.59; $P = .019$ for yes vs no), and primary genotype (HR, 1.72; $P = .024$ for genotypes 2, 3, or 4 vs genotype 1) were associated significantly with time to treatment initiation. By adding site to the fitted model, the intervention effect stayed similar and site showed a significant association with the time to treatment initiation (Palo Alto: HR, 0.43; $P = .008$; Bronx: HR, 0.57; $P = .037$). There was no significant interaction between site and intervention.

Treatment Adherence

Patients in the IC arm tended to show greater adherence to the planned therapy duration (Figure 3*A*). The mean percentage of treatment completion of planned duration was 70.3% (SD, 33.1%) in the IC arm and 61.7% (SD, 36.5%) in the UC arm. The proportion of patients completing at least 80% of planned treatment was 52% in the IC arm and 44% in the UC arm. The large majority of patients within the more than 80% adherence group completed 100% of the planned treatment duration in each arm (Figure 3*A*). Neither of these completion rates was significantly different between the 2 treatment groups. Of the patients completing less than 80% of the planned treatment duration in the IC and UC groups, reasons for early discontinuation included adverse event (39% and 44%, respectively), viral nonresponse (46% and 56%, respectively), and nonadherence (15% and 0%, respectively). Patients in the IC group tended to have higher rates of on-treatment virologic response at week 12, at the end of treatment, and in the follow-up time period, with final SVR rates of 50.0% in the IC and 41% in the UC arms (Figure 3*B*), however, these differences were not statistically significant.

Adverse Events

There was no significant difference in the number of serious adverse events between the IC and UC groups, although there was a trend toward fewer hospitalizations, emergency room visits, and deaths in the IC group compared with the UC group (Supplementary Table 1).

Protocol Adherence

Patients randomized to the IC arm had frequent contact with the midlevel mental health practitioner (Supplementary Table 2). There was no evidence of cross-contamination of mental health practitioner with patients randomized to the UC group at any site. Patients in the IC group had a greater number of visits to the hepatitis C clinic at each site compared with patients in the UC group.

Discussion

A large percentage of HCV patients have psychiatric and SUD comorbidities. A nationwide VA database analysis indicated that 85.4% of HCV patients had a psychiatric or SUD comorbidity, and 31% had an inpatient psychiatric or SUD hospitalization in the past year.[22] In non-VA clinics these comorbidities were cited as contraindications for antiviral therapy in 28% to 38% of patients.[11] Interferon-free regimens have greatly simplified treatment; however, high costs, limited access to care, and concerns about compliance continue to represent barriers to treatment for patients with these comorbidities.[13,14] The data presented indicate that an IC protocol using midlevel mental health providers for patients with hepatitis C and substance use and psychiatric comorbidities is effective, resulting in higher antiviral treatment rates and a 2-fold increase in the numbers of patients with a SVR.

Table 2. Simple Logistic Regression for the Association Between SVR and Baseline Characteristics

Baseline characteristics	*P* value	Odds ratio	95% confidence interval
Age	.90	1.004	0.95–1.06
BMI	.93	0.997	0.93–1.07
Race ethnicity			
African American		1.00	
White	.018	2.52	1.17–5.40
Hispanic	.73	1.20	0.42–3.40
Others	.84	1.18	0.24–5.73
Marital status			
Single		1.00	
Married	.77	1.19	0.38–3.74
Separated	.996	0.997	0.28–3.60
Divorced	.13	1.99	0.82–4.85
Widowed	.73	1.34	0.25–7.06
Education			
Grades 1–11		1.00	
High school	.96	1.03	0.35–3.01
Some college	.84	0.90	0.31–2.57
College or postgraduate	.25	0.37	0.07–2.02
Employment			
Employed		1.00	
Unemployed	.11	0.51	0.22–1.18
Homeless in past 5 years			
No		1.00	
Yes	.74	1.11	0.59–2.11
Genotype			
Type 1		1.00	
Types 2, 3, and 4	.014	2.38	1.19–4.74
PTSD risk			
No		1.00	
Yes	.95	0.98	0.51–1.88
HCV/HIV co-infection			
No		1.00	
Yes	.32	0.54	0.16–1.82
Screen AUDIT-C			
Negative		1.00	
Positive	.61	0.82	0.39–1.74
Screen BDI			
Negative		1.00	
Positive	.52	1.28	0.60–2.73
Previous substance abuse			
No		1.00	
Yes	.24	0.68	0.35–1.30
Prior medical illness			
No		1.00	
Yes	.48	0.79	0.41–1.52
Prior liver biopsy			
No		1.00	
Yes	.013	2.26	1.19–4.3
Prior psychiatric disorder			
No		1.00	
Yes	.013	0.44	0.23–0.84
Alcohol drinks at baseline month, n	.60	1.002	0.99–1.01
Active drug use at baseline			
No		1.00	
Yes	.04	0.50	0.25–0.97
Site			
San Diego		1.00	
Palo Alto	.06	0.43	0.18–1.03
Bronx	.006	0.32	0.14–0.73

AUDIT, alcohol use disorders identification test; BDI, Beck Depression Inventory; PTSD, post-traumatic stress disorder.

Table 3. Multivariate Regression Analysis

Variables	Odds ratio	95% confidence interval	*P* value
Association between SVR and intervention group			
Intervention group, IC vs UC	2.26	1.13–4.52	.022
Genotype, types 2, 3, 4 vs type 1	2.20	1.07–4.54	.033
Prior psychiatric disorder, yes vs no	0.44	0.22–0.86	.017
Active drug use, yes vs no	0.47	0.23–0.95	.034
	Hazard ratio		
Association between time to treatment initiation and intervention group			
Intervention group, IC vs UC	2.01	1.30–3.11	.002
Homeless in past 5 years, yes vs no	1.88	1.21–2.92	.005
Genotype, types 2, 3, and 4 vs type 1	1.72	1.07–2.75	.024
Active drug use, yes vs no	0.59	0.38–0.92	.019

The intervention was safe, with no significant differences in serious adverse events of death, hospitalization, and emergency room visits.

Multivariate logistic regression analysis of factors significantly associated with treatment initiation and SVR indicated that the IC intervention produced large effects (Table 3). We observed that a history of a prior psychiatric disorder and active drug use was significantly associated with less likelihood of having achieved an SVR on multivariate logistic regression. Subgroup analysis in patients with active drug or alcohol abuse at baseline, and patients without active substance abuse but with a risk for active psychiatric disease at baseline, showed that the IC intervention had positive effects on treatment initiation and SVR, respectively, in these groups (see the Supplementary Materials and Methods section). Interestingly, in contrast to non-VA studies, being homeless in the past 5 years at baseline was an independent predictor of initiating antiviral treatment (HR, 1.88; 95% confidence interval, 1.21–2.92; $P = .005$). This likely was due to the existence of robust homeless outreach programs in the VA that bundle housing, social services, and medical care. Approximately 70% of homeless veterans were receiving services from long-term homeless shelters, including on-site individual, peer-based, and group counseling; individual case management; vocational rehabilitation; classes and school opportunities; and transportation for clinic visits. These include services that nonhomeless veterans do not receive. This additional support is hypothesized as enhancing antiviral treatment initiation and completion.

Although IC has been well studied in primary care settings related to SUD, depression, and HIV, the IC models are not well studied in specialty care and few have focused on impactful clinical outcomes.[15,23,24]

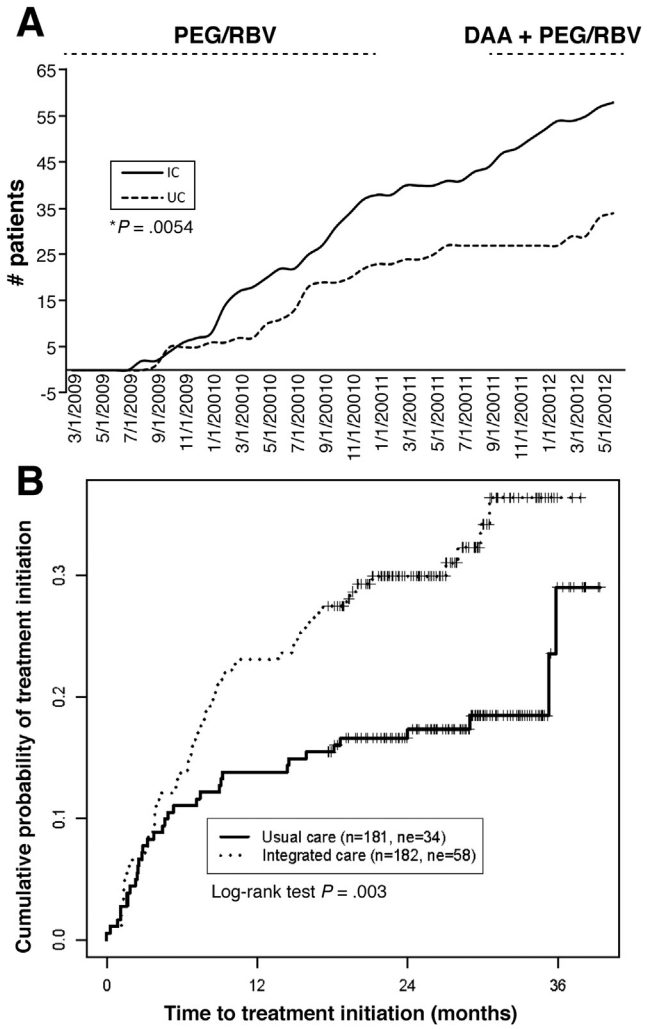

Figure 2. (*A*) Antiviral treatment initiation over time in the IC vs the UC group. Antiviral treatment periods are indicated for PEG + RBV and DAA + PEG + RBV. The y-axis shows the cumulative number of patients initiating treatment. Final treatment initiation rates were as follows: IC, 58 of 182 (31.9%); UC, 34 of 181 (18.8%) ($P = .005$). (*B*) Cumulative probability of treatment initiation by treatment group over time (months). Patients were censored at the end of the study follow-up period. ne, number of events (treatment initiation); PEG, pegylated interferon alfa; RBV, ribavirin.

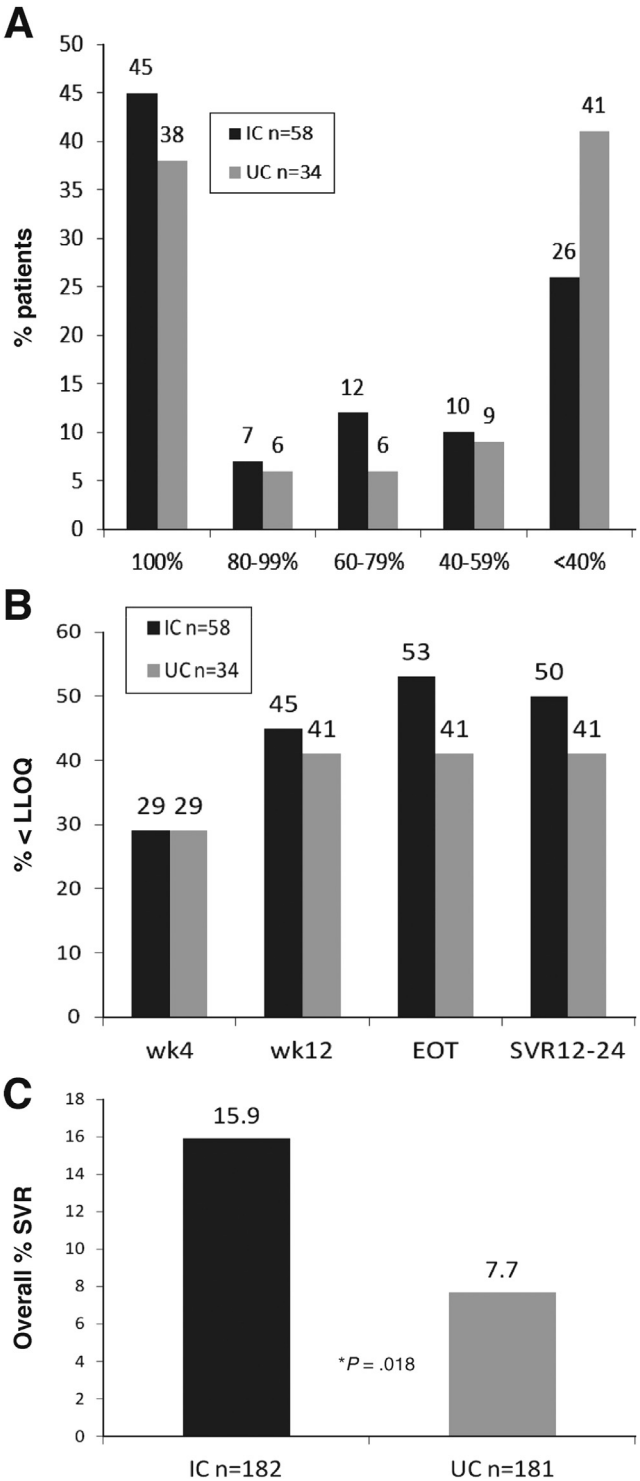

Figure 3. Adherence to planned therapy and virologic outcomes in IC vs UC. (*A*) Amount of adherence to planned duration of therapy. The percentage of treated patients who adhered to the indicated percentage of planned therapy. (*B*) On-treatment virologic response and SVR at 12 or 24 weeks for patients initiating therapy. LLOQ, lower limit of quantification. (*C*) Overall percentage of patients with SVR in each group.

Previous studies of patients with chronic hepatitis C and substance use and/or psychiatric comorbidities have been descriptive, and suggested that multidisciplinary care is feasible and safe,[25–28] or may lead to increased treatment candidacy.[29]

The mechanism of the increased antiviral treatment rates and SVR in the integrated arm could not be specified in this study owing to the multiple components that were included in IC. These included elements of case management and linkage to care, self-management, symptom control, substance use treatment, education and motivation, side-effect management, and access issues and co-located care. Multicomponent interventions evolved out of the recognition that single-component interventions often were ineffective. As a result, there have been few studies that rigorously examined each component of an integrated intervention.[24] A recent modeling study of hypothetical integrated care programs for HCV care found that multicomponent interventions provided better outcomes and more value for the money

than less costly interventions targeting single components.[30] We did observe a trend toward greater engagement of care at multiple levels in IC patients. This included an increased number of visits to the hepatitis clinics, an increased number of liver biopsies after enrollment, higher adherence to planned duration of therapy once started on antiviral treatment, and generally lower rates of all adverse events. None of these observed differences reached statistical significance, but were all in the direction favoring IC. It is possible that physicians simply were more comfortable treating the higher-risk HCV patients because they knew they were receiving integrated care including case management.

Our study had a number of limitations, including the fact that the patients and providers were not blinded to the intervention using the IC practitioner. Cross-contamination between treatment arms was possible, however, the IC practitioner never interacted with patients randomized to the UC comparison group. If cross-contamination had occurred and physician involvement with the IC midlevel practitioner influenced his/her care of patients assigned to the UC arm, this likely would have increased antiviral treatment processes in the UC group, biasing the study toward the null hypothesis, and strengthening our conclusions. The study was limited to VA patients, who predominantly are male, and therefore the results are less applicable to community practices. Finally, the study was conducted during a time when antiviral treatments for HCV were changing to include DAA treatments, which slowed treatment rates over the period of transition.

To optimize the public health impact of antiviral treatments for HCV, the number of patients who are able to receive these treatments must be expanded. New interferon-free regimens have fewer side effects and are expected to expand treatment populations to include a broader range of patients, many with very significant psychiatric and substance abuse disorders. These data suggest that integrated care for hepatitis C patients is one tool to maximize the access and success of antiviral treatment across a broad patient population.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.02.022.

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Conflicts of interest
These authors disclose the following: Samuel Ho has received research and grant support from Genetech, Inc, and Gilead Sciences, has served on the advisory board for Janssen Pharmaceuticals, Inc, and has served on the speakers bureau for Prime Education, Inc; Norbert Brau has received research and grant support from Gilead Sciences, BMS, Vertex, and AbbVie, has served on the advisory boards for Janssen Pharmaceuticals, Inc, and Gilead Sciences, and has served on the speakers bureau for Prime Education, Inc; Ramsey Cheung has received research and grant support from Gilead Sciences, and has served on the advisory board for Janssen Pharmaceuticals, Inc. The remaining authors disclose no conflicts.

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Supplementary Materials and Methods

Screening Tests

The tests used to screen patients for eligibility in the study were described previously.[1] These inclusion criteria included a Beck Depression Inventory score of 10 or greater, an alcohol use disorders identification test-C score of 4 or higher, a positive post-traumatic stress disorder-VA Primary Care screen or PTSD Checklist (PCL) (endorsement of $\geq$3 items), and/or drug use consisting of self-reported illicit drug use (illicit drugs other than marijuana and prescription drug abuse) within the previous 6 months. Patients scoring higher than the validated cut-off levels for any of these conditions were candidates for the study. For depression screening the original Beck Depression Inventory was used as updated in 1979.[2] Studies have indicated a high correlation of the Beck Depression Inventory and the later Beck Depression Inventory II test.[3] The diagnostic accuracy of the Beck Depression Inventory for clinical depression is 82% and higher as expressed by the area under the receiver operating characteristics curve, with sensitivities and specificities generally exceeding 80%.[4,5] For post-traumatic stress disorder we used the primary care post-traumatic stress disorder screen, a 4-question tool that at a cut-off score of 3 or higher has been shown to have a sensitivity and specificity of 78% and 87%, respectively, for the diagnosis of post-traumatic stress disorder.[6] Screening for illicit drug use (not including marijuana) included a drug use questionnaire that screened for drug use in the previous 6 months. Patients testing positive for this screening test completed questionnaires that evaluated drug use within the preceding 1 year and charts were audited for positive urine toxicology screens. The alcohol use disorders identification test-C was used to identify patients with high-risk alcohol use, with a cut-off score of greater than 4, as indicated by national VA guidelines (www.hepatitis.va.gov/provider/tools/audit-c.asp). This score will identify 86% of patients with heavy drinking and/or active alcohol abuse or dependency (sensitivity) with a specificity of 72%.[7]

Intervention

Integrated care protocol. The mental health providers in the study included 1 marriage and family therapist and 2 psychologists. All received uniform training in person at the beginning of the study and a written protocol and therapy manual. They had no prior experience with hepatitis C patients and they remained in each clinic for the duration of the study. Ongoing training and monitoring during the study consisted of monthly conference calls and patient discussions designed to maintain uniformity of the protocol and approach. We used a concept of integrated care that included practitioners working together as a team across specialties and service lines. The addition of a mental health provider to the usual clinic and under the collaborative direction of the hepatitis C providers (rather than a supervisor not involved in the clinic), represents an example of this type of integrated care. Other aspects of integrated care include using a common protocol, having frequent communication and meetings, having collaborative and common goals for patient care (initiating successful antiviral therapy), all of which were facilitated by the MH provider. Descriptions of the IC protocol were published previously.[1,8] Parameters for antiviral treatment initiation for both IC and UC were the inclusion and exclusion criteria provided in the VA treatment guidelines in effect at the time of the study.[9] These guidelines were uniform for the VA system and served as guidance for clinicians at each site. Treatment initiation guidelines called for substance use, depression, and other psychiatric conditions to be stable, which was determined by the practitioners as per standard medical criteria.

Statistical Analysis

Sample size determination. By using preliminary data, we estimated that 15% of patients in the UC arm would receive treatment and 30% would achieve an SVR, resulting in an overall SVR of 4.5%. For the IC arm, we estimated that 35% of patients would initiate treatment and that 40% of those initiating treatment would achieve an SVR, resulting in an overall SVR of 14%. With the earlier-described assumptions and a 2-sided type I error of 0.05, there was at least 80% power to detect that difference with a total of 330 patients (110 per site). An enrollment of 360 subjects was targeted to account for attrition.

Baseline characteristics. Descriptive statistics were used to summarize baseline characteristics. Baseline characteristics were compared between the intervention groups using the Wilcoxon rank sum test, the chi-square test and the Fisher exact test were used for comparison.

Primary and secondary outcomes. Intent-to-treat analysis was performed for all clinical outcomes. Initially, the proportion of patients with SVR (primary study outcome) was compared between the UC and IC groups using a univariate Fisher exact test. Multivariate logistic regression was used to assess the difference in SVR between the 2 groups with adjustment for baseline characteristics. The association between baseline characteristics and SVR was assessed with univariate logistic regression first. The method of purposeful selection was used for the selection of covariates, with a P value less than .10 being kept in the final model.[10] The likelihood ratio test was used for model comparison. Influential observations were assessed using Cook statistics and leverages. The final model was fitted by excluding influential observations and compared with the original model.

The main secondary outcome of time to treatment initiation was analyzed using the log-rank test and visualized with a Kaplan–Meier curve. Cox proportional

hazard modeling was used for multivariate analysis to adjust for baseline characteristics. The association between baseline characteristics and time to treatment initiation was assessed with univariate Cox regression as potential covariates in a multivariate model. Covariates for the final model were identified by purposeful selection. The partial likelihood ratio test was used for model comparison. The effects of influential observations on estimated parameters were assessed by score residuals[11] and the proportional hazards assumption was assessed using the test by Grambsch and Therneau.[12] The final multivariable Cox regression model was stratified by post-traumatic stress disorder risk owing to the violation of proportional hazards assumption. The influence of the study site and the interaction of the study site with the intervention arm was assessed in the fitted multivariate models for both SVR and treatment initiation. The percentage of treatment completion and the proportion of subjects completing 80% of treatment were compared between the 2 intervention groups using the Wilcoxon rank-sum test and the Fisher exact test. Adverse events were summarized by treatment group and compared using the Wilcoxon rank-sum test and the Fisher exact test. For subjects with and without active drug use at baseline and/or active alcohol abuse based on the alcohol use disorders identification test-C score at baseline, the differences in SVR, treatment initiation, and treatment completion between the UC and IC arms were compared using descriptive statistics and the appropriate univariate test such as the Fisher exact test and the Wilcoxon rank-sum test. All analyses were performed by SPSS (IBM, Armonk, NY) and R (Comprehensive R Archive Network), and a P value less than .05 was interpreted as statistically significant.

Subgroup Analyses: Subjects With and Without Active Drug and Alcohol Abuse

Among 234 subjects with active drug use and alcohol abuse at baseline, the IC intervention was associated significantly with treatment initiation (IC, 30.4%; UC, 16.4%; $P = .013$), but did not significantly affect the overall SVR rate in this group (IC, 10.7%; UC, 7.4%; $P = .49$). The mean adherence to the planned duration of treatment was 63.3% (SD, 34.3) for IC and 56.5% (SD, 39.5) for UC, and the proportion of patient completing at least 80% of the planned treatment was 41.2% in the IC and 45% in the UC arms. Neither of these completion rates was significantly different between the 2 intervention groups. Among 129 subjects with positive post-traumatic stress disorder risk and depression (Beck Depression Inventory, $\geq$10) but without active drug or alcohol abuse at baseline, the IC intervention was not associated significantly with treatment initiation (IC, 34.3%; UC, 23.7%; $P = .25$); but was associated with overall SVR (IC, 24.3% vs UC, 8.5%; $P = .020$). The mean adherence to the planned duration of treatment was 81.0% (SD, 27.5%) for the IC and 69.2% (SD, 31.5%) for the UC arm, and the proportion of patients completing at least 80% of the planned treatment was 62.5% in the IC and 42.9% in the UC arm. Neither of these completion rates was significantly different between the 2 intervention groups.

It should be noted that the study was not powered to detect significant differences in subgroups. In the subgroup of patients with active drug and alcohol abuse at baseline, more patients started treatment in IC, although the number of patients was low and a significant increase in SVR was not found. For the subgroup of patients at high risk for post-traumatic stress disorder and depression without substance abuse, IC was associated with a significant increase in the total number of patients achieving SVR, and we observed nonsignificant trends of increased treatment initiation and adherence in the IC group that may have contributed to the increase in SVRs observed in this subgroup.

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Supplementary Table 1. Adverse Event Outcomes (Number of Hospitalizations, Emergency Room Visits, and Death From any Cause) for Patients Randomized to the IC Group (n = 182 Unique Patients) or the UC Group (n = 181 Unique Patients)

	Total (n = 363), mean (SD)	IC (n = 182), mean (SD)	UC (n = 181), mean (SD)	*P* value
Number of hospitalization events/patient	0.89 (1.65)	0.79 (1.55)	0.99 (1.74)	.15
Number of hospital days/patient				
Subjects with a hospital event[a]	16.5 (37.2)	16.3 (42.5)	16.7 (31.7)	.13
All subjects[b]	0.98 (29.9)	9.38 (33.2)	10.3 (26.2)	.103
Number of ER visits/patient	2.99 (4.2)	2.85 (4.1)	3.14 (4.30)	.41
Number of deaths, n (%)[c]	22 (6.1)	8 (4.4)	14 (7.7)	.20

NOTE. The time period was from July 1, 2009, through August 1, 2012.
[a]There were 216 subjects (104 IC and 112 UC) with hospitalization events.
[b]Hospital day was 0 for subjects without a hospitalization event.
[c]Causes of death in the IC group were as follows: decompensated cirrhosis (2), cardiac arrest (1), medication overdose (1), cancer (1), unknown (3). No patients were receiving antiviral therapy. Causes of death in the UC group were as follows: decompensated cirrhosis (2), cancer (2), colitis (1), cardiac arrest (2), unknown (7). One of the unknown deaths occurred at 2 months on antiviral therapy.

Supplementary Table 2. Adherence to Protocol by Site for Clinic Visits With IC Mental Health Practitioner and for HCV Clinic Visits (Not Involving Mental Health)

	All sites	Bronx	Palo Alto	San Diego
Patients IC, n	182	63	41	78
Patients UC, n	181	61	41	79
IC mental health practitioner visits				
Integrated care (visits per patient)	1821 (10.0)	695 (11.03)	370 (9.02)	756 (9.69)
Usual care	0	0	0	0
Total HCV clinic visits (nonmental health)[a]				
Integrated care (visits per patient)	1670 (9.18)	507 (8.05)	208 (5.07)	955 (12.24)
Usual care (visits per patient)	1052 (5.82)	404 (6.62)	129 (3.15)	519 (6.57)
IC patients without antiviral treatment, n	124	48	33	43
UC patients without antiviral treatment, n	147	52	36	59
Total HCV clinic visits (nonmental health) for patients without antiviral treatment[b]				
Integrated care (visits per patient)	566 (4.57)	312 (6.50)	80 (2.42)	174 (4.05)
Usual care (visits per patient)	522 (3.55)	288 (5.54)	80 (2.22)	154 (2.61)

NOTE. The time period was from April 1, 2009, through July 31, 2012. Each site implemented a similar number of visits per patient in the IC arm.
[a]Includes clinic visits for all patients with or without antiviral treatment.
[b]Includes clinic visits for patients who never received antiviral treatment.