Process of Care for Hepatitis C Infection Is Linked to Treatment Outcome and Virologic Response

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BACKGROUND & AIMS: Process of care–based measures are used commonly to assess the quality of medical care provided to patients with chronic hepatitis C virus (HCV) infection. However, the links between these processes and patient outcomes are not clear. **METHODS:** We conducted a large retrospective cohort study of 34,749 patients with HCV infection identified from the national Veterans Administration HCV Clinical Case Registry between 2003 and 2006. We examined the relationship between meeting process–based measures of HCV care (categorized into pretreatment, preventive or comorbid care, and treatment monitoring domains) and antiviral treatment-related outcomes. For each domain, we defined optimum care as receipt of all indicated care processes in that domain. Study end points were rates of antiviral treatment, treatment completion, and sustained virologic response (SVR), adjusted for patient demographics, comorbidities, use of health services, and intrafacility clustering. **RESULTS:** Patients who received optimum pretreatment care were significantly more likely to receive antiviral treatment (odds ratio [OR], 3.2; 95% confidence interval [CI], 2.9–3.5), complete treatment (OR, 1.26; 95% CI, 1.13–1.43), and achieve an SVR (OR, 1.29; 95% CI, 1.01–1.65), than those with suboptimum pretreatment care. Optimum preventive or comorbidity care also independently was associated with receipt of antiviral treatment (OR, 1.36; 95% CI, 1.23–1.51), but not with completion of treatment or SVR. Optimum treatment monitoring was associated with a nonsignificant trend toward achieving an SVR (OR, 1.22; 95% CI, 0.95–1.56). **CONCLUSIONS: Optimum care for HCV infection—particularly the care delivered before treatment—is associated with increased rates of treatment and SVR. These data could be used to guide clinical policy as newer, more-effective treatments become available.**

Keywords: Quality of Care; Performance; Chronic Liver Disease; Indicator.

Chronic hepatitis C virus (HCV) infection is a common condition affecting 1.3% of the US population.[1,2] Beginning in the 1990s, randomized trials of interferon and ribavirin showed improvement in achieving viral eradication in patients with HCV,[3–8] and subsequent trials of direct-acting antivirals (DAAs) have proven even more successful.[9,10] Several professional societies have published protocols for the care of HCV patients, with recommendations covering the diagnostic workup, prevention and treatment of common comorbidities, and initiation and monitoring of antiviral therapy.[11,12] Despite these well-disseminated guidelines, data suggest that systematic deficiencies in HCV care exist.[13–15] Moreover, the relationship between following such recommendations and improved clinical outcomes in the real-world settings outside of clinical trials is not known.

As with other conditions, quality of HCV care can be quantified using process-based measures (eg, confirming viremia, testing HCV genotype) or outcome-based measures of care (eg, sustained virologic response [SVR], mortality).[16] Both are common elements in performance measurement sets. Process measures (PMs) have the advantage of requiring less risk adjustment because properly constructed specifications narrowly define the clinical circumstances for indicated care. Moreover, PMs are more directly under provider or system control, and thus are more direct targets for quality improvement efforts.[16] However, to be a meaningful measure of quality, a process-of-care measure should be related to patient outcomes (ie, have predictive validity for the desired outcome).[17] This relationship can be based on underlying trials or expert opinion. In HCV, trials do underlie many accepted standards (such as use of antiviral therapy and determining genotype before therapy), usually among highly selected populations, whereas others rely more on expert opinion (such as vaccination for hepatitis A and hepatitis B). Remarkably few studies empirically link process indicators to outcomes,[18,19] and none have done so in HCV.

We evaluated the relationship between adherence to a broad set of process-based measures in HCV and 3 subsequent HCV-specific end points: receipt of antiviral treatment, completion of antiviral treatment, and the clinical outcome associated with improved survival—SVR. Evaluating this process-outcome link is particularly important with the changing landscape of treatment in HCV. If process of care independently predicts treatment end points in HCV, then it would suggest that efforts targeted at improving the broader sweep of health care quality might be the key to fulfilling the promise of the new agents in clinical practice.

Abbreviations used in this paper: CI, confidence interval; DAA, direct-acting antiviral; HCV, hepatitis C virus; OR, odds ratio; PM, process measures; SVR, sustained virologic response; VA, Veteran's Affairs.

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Methods

Process-of-Care Measures

We measured process-based quality of care delivered to patients with HCV using 20 explicit PMs. A 9-member multidisciplinary expert panel derived these PMs using the RAND/University of California Los Angeles Appropriateness Method.[20] This method has been widely used to develop a process-based measure of health care quality in other areas of medicine and has been shown to have content, construct, and predictive validity.[21–25] Details of the HCV panel process and its results are described elsewhere.[26] The PMs covered 3 domains of care. Seven PMs measured pretreatment care that precedes antiviral treatment in HCV (confirmation of HCV viremia, evaluation by HCV specialists, HCV genotype testing, liver biopsy in genotype 1 patients, and ruling out hepatitis B, autoimmune, and iron overload–related liver diseases); 7 PMs measured prevention-related and management of comorbid conditions–related care (human immunodeficiency virus testing, hepatitis A and B serology testing and vaccination if negative serology, treatment of depression, and treatment of substance use disorder); and 6 PMs measured treatment monitoring–related care (testing viral load before, at week 12, at week 24, at week 48 [for genotype 1], reducing ribavirin dose for anemia during antiviral treatment, and not prescribing growth-stimulating factors for leukopenia during antiviral treatment). Supplementary Table 1 contains the list of measures used in our study.

Data Source

We identified our study cohort from the Veterans Administration HCV Clinical Case Registry.[27] This database contains health care use and clinical data for more than 300,000 patients with HCV. Data elements include demographics, all laboratory tests with results, outpatient and inpatient pharmacy data, and inpatient and outpatient use in the form of International Classification of Diseases, 9th revision and Current Procedural Terminology codes.

Study Cohort

Our study cohort comprised patients who had their first positive HCV laboratory test (antibody, polymerase chain reaction, or genotype) after December 2002 and had at least 2 years of follow-up evaluation before December 2006. Patients had to be older than 18 years at the time of HCV diagnosis, eligible for at least one of the HCV PMs, and have active viremia to be included in this analysis.

We applied the HCV PMs to our study cohort. For each PM, we developed specifications for measurement based on a combination of sources (International Classification of Diseases, 9th revision codes, Current Procedural Terminology codes, laboratory data, and so forth) in the database. For each subject, we determined if she/he was eligible for the process specified in each PM (Supplementary Table 1). We then determined if she/he received the care recommended by the PM. Supplementary Table 1 also contains the operational definition, number of eligible patients, and the pass rate for each measure.

Definition of Study Variables

Hepatitis C virus process measures and aggregate scores. We calculated each PM rate as the percentage of patients who received the care indicated by the PM out of all eligible patients. We then calculated 3 domain-specific HCV process scores; each as the percentage of recommended HCV PMs in each domain that an eligible patient received. Thus, each patient had a pretreatment care domain score, preventive/comorbid-related care domain score, and, in patients who received antiviral treatment, a treatment monitoring care domain score. For each patient and each domain, we then created an indicator for whether a patient received all recommended care in the domain for which she/he was eligible (optimum care) for each.

Study end points (outcomes). We examined 3 sequential end points: receipt of antiviral treatment, completion of antiviral treatment, and SVR.

We defined antiviral treatment as at least one filled prescription of interferon. For patients who received multiple courses of treatment, we examined only their first course for this analysis.

We defined treatment duration by calculating the cumulative days of supply of interferon prescriptions as previously defined.[28] Because patients in the clinical setting may have a shorter treatment course, we defined patients who completed at least 80% of expected treatment duration to have completed therapy as done in a previous study (ie, 38.4 weeks for genotypes 1 or 4 and 19.2 weeks for genotypes 2 or 3).[29]

We defined SVR as all RNA tests being negative after treatment completion with one being recorded at least 12 weeks after treatment completion.[28]

Statistical Analysis

We first examined the bivariate associations between meeting individual PMs and each of the study end points. We then conducted bivariate followed by multivariable logistic regression analyses to examine the overall domain effect on study outcomes.

In the first multivariable regression model, receipt of antiviral treatment was the dependent variable and the primary regressors were pretreatment and preventive/comorbid care optimum care indicators. This model was applied to patients who were eligible for at least one HCV PM. In the second regression model, treatment completion was the dependent variable and the main regressors were the same as described earlier. This model was applied only to those patients who started antiviral treatment before July 2005 (this ensured that all patients had more than 24 weeks of follow-up evaluation after their treatment course to allow ascertainment of treatment completion and SVR). In the third model, SVR was the dependent variable and the main regressors included 3 domains of HCV care. The third regression model was applied only to those patients who completed antiviral treatment.

We added the following covariates in the regression models: demographic characteristics (age, race), use of health care (number of medical visits per quarter), HCV genotype, diagnosis of cirrhosis, comorbid depression, drug or alcohol use, and presence of medical comorbidity that constituted potential contraindications to antiviral treatment on the basis of the American Association for the Study of Liver Disease guidelines. These included severe heart failure, chronic pulmonary obstructive disease, active coronary artery disease, severe hypertension or diabetes, and renal failure, as previously described.[30]

To take into account the fact that patients seen in the same facility tend to receive similar care, we assigned each patient a regular facility where she/he was seen most frequently, and

adjusted the covariance matrix for intrafacility correlation using the generalized estimating equation method.

The results of these multivariable models are presented as odds ratios (OR) along with 95% confidence intervals (CIs). All analyses were conducted using SAS (version 9.2; SAS Institute, Cary, NC).

Sensitivity analyses. We conducted several sensitivity analyses. First, it is plausible that physicians may provide better care to patients who are likely to have better outcomes based on their baseline characteristics. This selection bias would result in higher care (particularly that occurring pretreatment) being related to higher rate of treatment. To address this, we reconstructed the treatment initiation model after excluding from our overall nationwide sample patients who met any of the treatment exclusions based on the contraindications specified in the American Association for the Study of Liver Disease guidelines.[31] We used administrative and clinical data to define the presence of exclusions, as previously described.[30] Because this approach might have missed several factors that could preclude treatment, such as patient's noninterest in treatment and physicians' assessment of the risk/benefit ratio associated with antiviral treatment for a given patient, we used data from a structured chart review of a random sample of 571 HCV viremic patients receiving care at 4 large Veteran's Affairs (VA) facilities. For patients who did not meet PMs, we determined if the nonadherence was related to possibly justifiable exceptions including providers' perception of patients' comorbidities, patients' refusal, or receipt of care outside the VA. Using the chart review data, we recalculated the PM rates (and domain scores) by excluding patients with these possible exceptions from the PMs, and re-ran the treatment initiation models. Last, we changed the specifications of several PMs to determine if the alternative definitions would impact our results. These included removing patients with cirrhosis from the liver biopsy PM, reconstructing the depression PM to include only patients who developed depression while on antiviral treatment, extending the time frame for human immunodeficiency virus testing PM, and restricting the time frame for confirmation of HCV viremia PM.

Results

Demographics and Clinical Characteristics

We identified 34,749 patients who were eligible for inclusion in the study cohort (Table 1). Their mean age was 52.9 years (standard deviation, 9.1 y); 97% were male, 49% were white, and 26% were African Americans. Most of the patients had 3 or more visits to the VA per quarter. Approximately half of the patients had HCV genotype 1, 13% had HCV genotypes 2 or 3, and most of the remaining patients did not receive an HCV genotype test. Twelve percent had cirrhosis and 25.9% had depression. Each patient was, on average, eligible for 4.8 pretreatment, 2.7 treatment, and 5.2 prevention or comorbid condition care measures. Of the patients analyzed, 6224 received antiviral treatment. Of the patients who started antiviral treatment, 49% completed treatment and 32% had SVR.

Overall, 11% (n = 3905) of patients received all indicated pretreatment care and 8% (n = 2798) received all indicated preventive/comorbid condition care. Among those who received antiviral treatment, 37% (n = 2309) received all indicated treatment monitoring care.

Table 1. Characteristics of 34,749 Patients With Chronic HCV Infection Who Were Eligible for at Least One Process-of-Care Measure

Variables	Distribution, % (n)
Demographics	
Age, *y*	
<45	13.6 (4715)
46–55	61.1 (21,223)
56–65	20.2 (7024)
>65	5.1 (1787)
Male	96.6 (33,579)
Race	
White	49.2 (17,085)
African American	26.1 (9060)
Other race	1.3 (347)
Unknown	23.45 (8150)
Health care use	
Visits per quarter	
<3	44.1 (15,334)
≥3	55.9 (19,415)
Follow-up period, *y* (mean, SD)	3.6 (0.9)
Clinical characteristics, %	
HCV genotype	
1 or 4	51.1 (17,746)
2 or 3	13.4 (4646)
Unknown	35.6 (12,357)
Cirrhosis[a]	12.4 (4308)
Depression[b]	25.9 (8991)
Drug or alcohol use	51.48 (17,890)
Comorbidity[c]	15.7 (5449)
Number of PMs for which patients were eligible, mean (SD)	
Pretreatment care	4.8 (2.2)
Treatment-related care (if received treatment)	2.7 (1.2)
Prevention-related care	5.2 (1.2)

[a]We defined cirrhosis based on the presence of cirrhosis-related International Classification of Diseases, 9th revision (ICD-9) codes (571.2, 571.5) within 1 year of the HCV index date.
[b]Depression was defined on the basis of ICD-9 revision codes for depression (296.2, 296.3, 300.4, 311) within 1 year of the HCV index date. Drug and alcohol use defined on the basis of ICD-9 codes (291.xx, 292.xx, 304.xx, 305.0x, 305.2–305.9, 648.3x, 655.5x, 760.71–760.73, 760.75, 779.5x, 965.0x, 980.0x, V65.42, and 303.xx). In addition, we looked for laboratory evidence of illicit drug use and alcohol use based on blood levels for these agents.
[c]Comorbidity was defined as any of the following: severe hypertension, heart failure, coronary artery disease, poorly controlled diabetes, severe chronic obstructive pulmonary disease, or chronic renal disease.

Hepatitis C Virus Treatment End Points When Receiving Recommended Care vs Not Receiving Recommended Care by Individual Process Measures

For all the measures in the pretreatment and preventive/comorbid care domains, patients who received recommended care were more likely to initiate treatment, complete treatment, and achieve SVR, although some of these differences were not statistically significant (Table 2). Specifically, patients

Table 2. HCV Treatment End Points When Receiving Recommended Care vs Not Receiving Recommended Care by Individual PMs

	Treatment receipt			Treatment completion			SVR		
Process measures	Eligible patients, n	Treatment initiation if received recommended care, %	Treatment initiation if did not receive recommended care, %	Eligible patients, n	Treatment completion if received recommended care, %	Treatment completion if did not receive recommended care, %	Eligible patients, n	SVR if received recommended care, %	SVR if did not receive recommended care, %
Pretreatment care									
Confirmation of HCV viremia	31,193	**17.7**	**9.7**	4856	**49.3**	**38.4**	1443	48.5	48.9
Specialty evaluation	34,212	**27**	**7.8**	5546	**49.8**	**44.1**	1669	48.8	44.7
Hepatitis B testing	22,022	**25.2**	**22.5**	4930	48.8	47.7	1498	48	46.6
Autoimmune liver disease testing	22,022	**31.4**	**17.4**	4930	49.1	47.9	1498	**50.6**	**41.2**
Iron overload testing	22,022	**28.6**	**15.9**	4930	**49.6**	**44.4**	1498	48.3	45.5
HCV genotype testing	21,640	**30.5**	**8.6**	4902	**49.5**	**36.9**	1492	**48.4**	**32.4**
Liver biopsy in genotype 1	13,268	**46.3**	**20**	3296	**43.8**	**40.1**	884	**46**	**37.2**
Optimum care	34,749	**44.6**	**14.5**	6224	**57.4**	**46.2**	1971	**57.6**	**43.3**
Preventive and comorbid condition care									
HIV testing	34,265	**22.2**	**16.4**	5513	**46.3**	**50**	1667	50.7	47.1
Hepatitis A serology testing	32,881	**20.4**	**12.8**	5273	49	46.9	1571	49.3	44.4
Hepatitis B serology testing	31,257	**19.4**	**11.6**	5020	49	44.7	1485	48.6	45.7
Hepatitis A vaccination	26,171	**27.8**	**13.7**	4033	**53.6**	**46.4**	1228	**53**	**45.8**
Hepatitis B vaccination	22,863	**27.2**	**13.3**	3566	**52.9**	**45.9**	1092	**53.4**	**47.4**
Depression care	13,326	20.8	21.4	2514	48.6	48.4	782	52.7	45.6
Substance use care	18,637	**13.5**	**15.2**	2479	**42**	**47.7**	688	51.2	46.7
Optimum care	34,749	**27.6**	**17.1**	6224	48.5	49.5	1971	48.5	48.1
Treatment-related care									
RNA testing before treatment	—	—	—	5559	**50.4**	**44.5**	1674	48.2	48.7
RNA testing at week 12	—	—	—	4363	62.6	61.2	1676	**50.5**	**44.8**
RNA testing at week 24	—	—	—	—	—	—	1493	48.5	45.6
RNA testing at week 48	—	—	—	—	—	—	695	40.7	35
Decreasing ribavirin if anemia	—	—	—	842	**52.6**	**62.3**	321	42.6	54.6
No growth factors if low neutrophils	—	—	—	503	57.8	64.3	187	50.4	46.8
Optimum care	—	—	—	—	—	—	1971	49.2	47.7

NOTE. Bolded values indicate statistical significance at an α value of .05. RNA testing at weeks 24 and 48 was not applicable for treatment completion because these time points correlated with the cut-off values that we used to ascertain treatment completion.
HIV, human immunodeficiency virus; NA, not applicable.

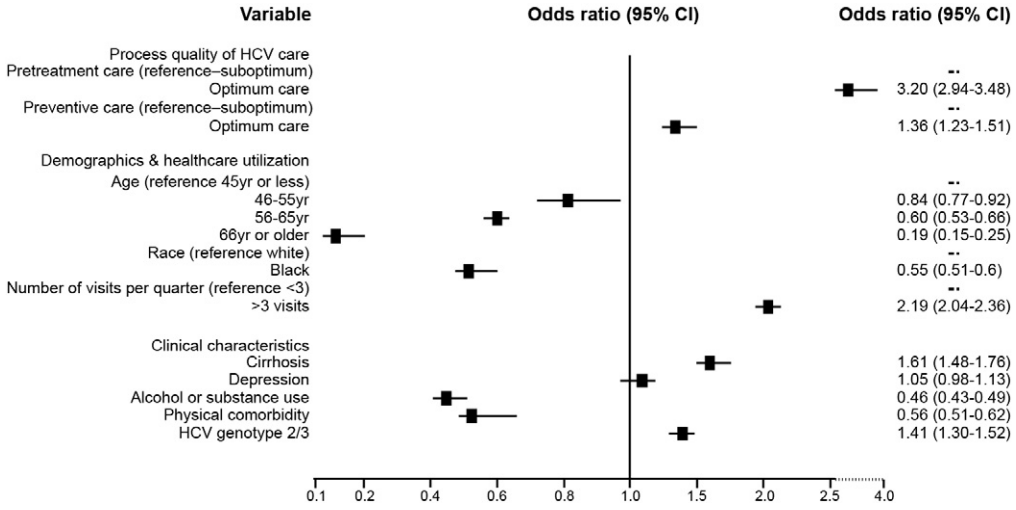

Figure 1. Association of process of HCV care with antiviral treatment receipt: results of multivariable analyses.

who met the HCV genotype testing and liver biopsy for genotype 1 HCV measures had higher rates of treatment initiation (30.5% vs 8.6% and 46.3% vs 20%, respectively), treatment completion (49.5% vs 36.9% and 43.8% vs 32.4%, respectively), and SVR (48.4% vs 32.4% and 46% vs 37.2%, respectively) than those who did not meet these measures. Patients meeting the measure of seeing the HCV specialists were more likely to initiate treatment (27% vs 7.8%), and, once started, were more likely to complete treatment (49.8% vs 44.1%) than those who did not. However, there were a few exceptions. Patients who received recommended care for substance use disorders had slightly lower rates of antiviral treatment initiation (13.5% vs 15.2%) and completion (42.0% vs 47.7%) than those who did not. Patients who had the recommended ribavirin dose reduction (to manage treatment-induced anemia) were significantly less likely to complete treatment (52.6% vs 62.3%) and achieve SVR (42.6% vs 54.6%) than those who did not have their ribavirin dose reduced.

Table 2 also displays the bivariate associations between domain-specific aggregate score and each of the study end points.

Association Between Process of Hepatitis C Virus Care and Antiviral Treatment Receipt

Patients with optimum pretreatment care had 3.2-fold higher odds of receiving antiviral treatment than those with suboptimum pretreatment care (Figure 1). Independent of pretreatment care, patients receiving optimum preventive and comorbid conditions care had significantly higher (+36%) antiviral treatment rates than patients with suboptimum care.

Sensitivity analyses with restricting the sample to patients without treatment exclusions did not change the direction or magnitude of association between treatment initiation and pretreatment care (OR, 2.88; 95% CI, 2.57–3.24) or preventive/comorbid care (OR, 1.42; 95% CI, 1.21–1.65), respectively. Similarly, use of PM data derived from medical chart reviews did not change the direction of the effect (OR for pretreatment care and preventive/comorbid care were 1.84 and 2.38, respectively), although the estimates were not statistically significant because of power limitations in this analysis (Supplementary Table 2).

Association Between Process of Hepatitis C Virus Care and Antiviral Treatment Completion

Among all treated patients, we found a significant association between pretreatment care and antiviral treatment completion. The odds of completing treatment were 26% higher in patients who received optimum care pretreatment than those who did not (Figure 2). Optimum preventive and comorbid care was not associated with treatment completion.

Association Between Process of Hepatitis C Virus Care and Sustained Virologic Response

Patients with optimum pretreatment care had higher odds of achieving SVR than those with suboptimum pretreatment care (OR, 1.30; 95% CI, 1.01–1.66) (Figure 3). Preventive and comorbid conditions care was not associated with SVR in patients who received and completed antiviral treatment. There was also no difference in the SVR between patients receiving optimum vs suboptimum monitoring during treatment. However, given the known strong positive association between ribavirin dose and SVR,[32,33] we removed the ribavirin dose reduction measure from the treatment monitoring domain and reconstructed the models predicting SVR. With this, the odds of achieving SVR were 22% higher for patients who received optimum treatment monitoring care than those who did not (OR, 1.22; 95% CI, 0.95–1.56), although the estimate was not statistically significant.

Changing the specification of the PMs did not change the results (data not shown).

Discussion

We found that better performance on the HCV process-of-care measures was associated with what patients with HCV and their providers care about most: the receipt of potentially curative antiviral treatment and its outcomes. This relationship was most pronounced for the care processes that occurred before antiviral treatment, such as those related to the diagnosis and evaluation of HCV. Specifically, we found that the odds of starting antiviral treatment were 3-fold higher for patients who received optimum pretreatment (ie, diagnosis and evaluation-

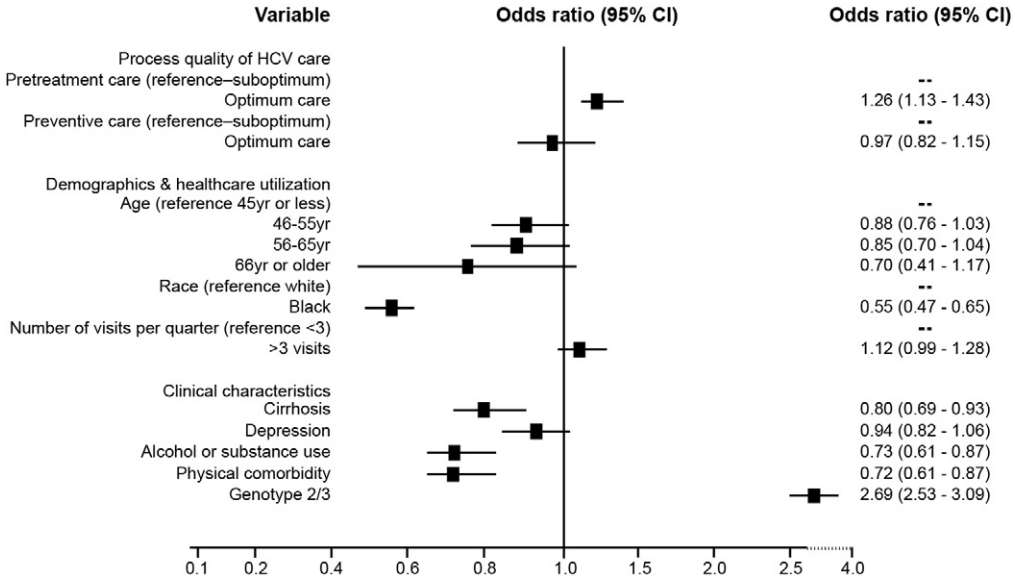

Figure 2. Association of process of HCV care with treatment completion: results of multivariable analyses. This analysis was limited to patients who started antiviral treatment. Treatment start date had to be before July 2005 to allow adequate follow-up evaluation for all patients.

related) care than those who received suboptimum care. Moreover, among patients who initiated antiviral treatment, the process of care that they received before their treatment strongly predicted completion of the assigned treatment course as well as subsequent SVR. Although we also found a trend toward higher SVR in patients who received better treatment monitoring care, this did not reach statistical significance, suggesting that most of the effect of HCV care process on SVR may indeed be mediated through receipt of, and, when initiated, the completion of, antiviral treatment.

The evidence supporting many PMs included in this analysis, combined with the moderately strong association that we found, and the temporal relationship between the evaluated care and subsequent treatment and outcomes, collectively suggest that we have identified important links in the chain that leads to better HCV outcomes. Some of the PMs—particularly those in the pretreatment care group—may begin a pathway to processes that then improve treatment rates (such as the effect of specialty evaluation on antiviral treatment). Others may not lead directly to treatment outcomes but may be markers of comprehensive medical care or more compliant patients, which in turn is related to better outcomes. This would explain the positive association between comorbid and preventive care and receipt of antiviral treatment. Similarly, this would explain the persistent effect of process of care that patients received before starting treatment on treatment completion and SVR (Figures 2 and 3).

The relationship between individual measures and our study end points sheds light on the underlying mechanisms of the process-outcome link in HCV (Table 2). With few exceptions, we found consistently positive associations between all measures and treatment end points, although some of these associations were stronger than others. Given this strong effect, we considered the possibility of confounding by indication, such as pro-

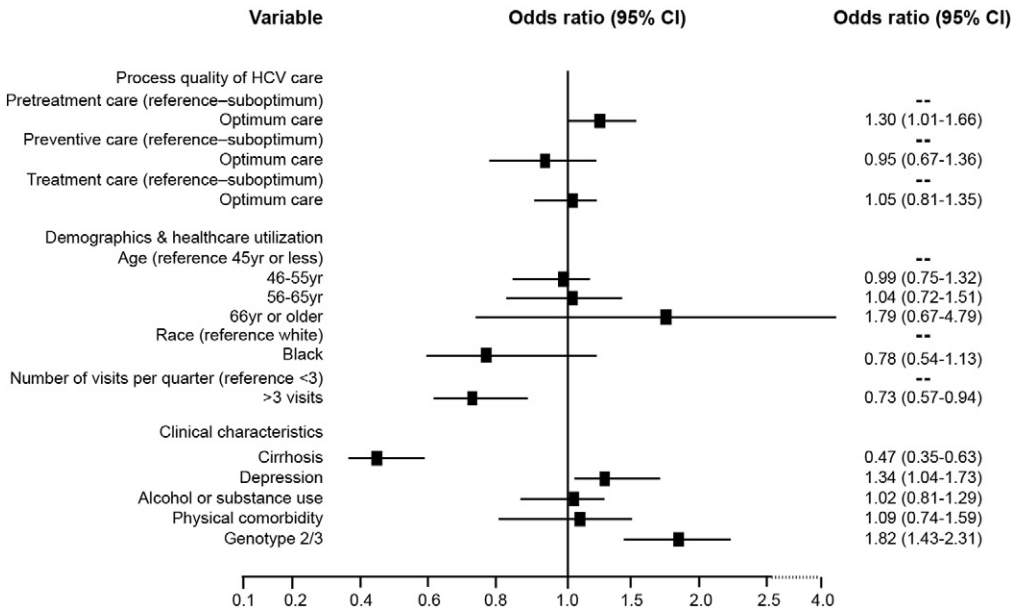

Figure 3. Association of process of HCV care with SVR: results of multivariable analyses. This analysis was limited to patients who completed antiviral treatment.

viders' perceptions of treatment eligibility and patients' preference for treatment. For example, it is plausible that patients who received a genotype test or those who underwent a liver biopsy did so because they were good candidates for antiviral treatment or because they had strong preference for treatment. Providers' assessments of patient-specific risk/benefit ratio and patients' preferences are not documented in the database, and therefore, we could not account for these in this study. In our previous study, we found that a significant proportion of patients had possible exceptions (due to comorbidity, patient refusal, etc) to several measures, which might result in an underestimation of these measures. To address this, we performed 2 separate sensitivity analyses to define more narrowly circumstances of care by excluding patients with potential treatment contraindications and then by limiting the analysis to our chart review subsample with chart-documented data on patient-specific risks and preferences for treatment. The positive association between meeting the PMs and treatment end points remained in these highly selected groups of patients, providing further support to the observed process-outcome link in HCV. Collectively, our data lend support to the validity of the initiatives that motivate quality measurement using these process-based measures for patients with HCV.[34]

The implications of our data are important to the present and future of HCV management. Two new DAA agents have become available and, when given in combination with pegylated interferon and ribavirin, significantly increase the cure rates in HCV patients in randomized clinical trials.[9,10] However, the effectiveness of DAA likely will be offset by new challenges in real-world practice. Advanced physical and mental comorbidity continue to contraindicate the use of DAA. Once treatment is started, there is a greater risk of viral resistance and significantly more frequent and more severe adverse events than combination interferon and ribavirin therapy. Given the independent association between HCV PMs and treatment end points, our data suggest that efforts targeted at improving HCV care—particularly the care delivered before antiviral treatment—might be a way to fulfill the promise of these new agents as they become widely disseminated in routine clinical practice. We also found that after accounting for the pretreatment care, patients with cirrhosis and genotype 2 or 3 HCV infection were more likely to receive treatment. Similarly, as expected, we found that genotype 2/3 infection was the strongest predictor of completion of treatment, likely because of the shorter duration of treatment and the higher rate of response. These data show that factors other than the process of HCV care (such as expected duration of treatment, side effects of medications, and predicted likelihood of response) are important and will likely remain so in deciding who will be treated in the era of DAAs.

Our study had several limitations. Despite being comprehensive, the HCV PM set did not capture all aspects of HCV care. Some examples include counseling regarding alcohol use and care targeting patients with post-traumatic stress disorder and anxiety. Nonetheless, we believe that the measure set addresses critical areas of care in HCV and emulate those targeted by contemporary practice guidelines. Moreover, we could not ascertain patients' and physicians' knowledge, attitudes, and perceptions regarding antiviral treatment—data that would need qualitative evaluations. Our cohort included only HCV patients who used the VA, thus potentially limiting the applicability of our results to other systems of care. However, similar reported results for common PMs in other systems[13] speak to greater generalizability. It is plausible that the processes of HCV care might have improved significantly since 2006 and these may change further with the introduction of new drugs. However, the association between optimum care and improved outcomes remains relevant. Some of our findings may appear counterintuitive. Patients with treatment-induced anemia who had their ribavirin dose reduced were less likely to achieve SVR than those who did not. Given that dose reductions in ribavirin may affect treatment efficacy, the observed association between ribavirin dose reduction PM and treatment end points is biologically plausible.[32,33] Future applications, therefore, might exclude this measure from the HCV set. Patients who received the recommended substance use treatment were less likely to start and complete antiviral treatment than those who did not. Patients who met this measure (ie, referred to specialty mental health) might have more significant problems with substance use, whereas those with milder substance abuse might have been capable of achieving remission without substance abuse referral.

Our data show that when patients receive the recommended HCV care, they get treated and have better responses more often. An important next step is to evaluate whether interventions can be implemented that improve the delivery of these care processes to patients with HCV and whether these improvements lead, as our results suggest, to improvements in outcomes in HCV. Our data also suggest that efforts targeted at improving HCV process quality may be a way to fulfill the promise of the new DAA agents as they become widely disseminated in routine clinical practice.

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.2012.07.015.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–714.
2. Kim WR, Brown RS Jr, Terrault NA, et al. Burden of liver disease in the United States: summary of a workshop. Hepatology 2002; 36:227–242.
3. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998;352:1426–1432.
4. Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1493–1499.
5. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–982.
6. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–965.
7. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-

alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–355.
8. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303–1313.
9. Jacobson IM, McHutchison JG, Dusheiko G, et al. ADVANCE study team. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405–2416.
10. Poordad F, McCone J Jr, Bacon BR, et al. SPRINT-2 investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195–1206.
11. Ghany MG, Strader DB, Thomas DL, et al. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–1374.
12. Seeff LB, Hoofnagle JH. National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. Hepatology 2002;36(Suppl 1):S1–S2.
13. Kanwal F, Schnitzler MS, Bacon BR, et al. Quality of care in patients with chronic hepatitis C virus infection: a cohort study. Ann Intern Med 2010;153:231–239.
14. Kramer JR, Hachem CY, Kanwal F, et al. Meeting vaccination quality measures for hepatitis A and B virus in patients with chronic hepatitis C infection. Hepatology 2011;53:42–52.
15. Butt AA, Justice AC, Skanderson M, et al. Rate and predictors of treatment prescription for hepatitis C. Gut 2007;56:385–389.
16. McGlynn EA, Asch SM. Developing a clinical performance measure. Am J Prev Med 1998;14(Suppl):14–21.
17. Brook RH, McGlynn EA, Cleary PD. Quality of health care. part 2: measuring quality of care. N Engl J Med 1996;335:966–970.
18. Asch SM, McGlynn EA, Hiatt L, et al. Quality of care for hypertension in the United States. BMC Cardiovasc Disord 2005;5:1.
19. Higashi T, Shekelle PG, Adams JL, et al. Quality of care is associated with survival in vulnerable older patients. Ann Intern Med 2005;143:274–281.
20. Fitch K, Bernstein SJ, Aguilar MS. The RAND/UCLA appropriateness method user's manual. California: RAND, 2001.
21. McGory ML, Kao KK, Shekelle PG, et al. Developing quality indicators for elderly surgical patients. Ann Surg 2009;250:338–347.
22. Maggard MA, McGory ML, Shekelle PG, et al. Quality indicators in bariatric surgery: improving quality of care. Surg Obes Relat Dis 2006;2:423–429.
23. Shekelle PG, MacLean CH, Morton SC, et al. Acove quality indicators. Ann Intern Med 2001;135:653–667.
24. MacLean CH, Louie R, Leake B, et al. Quality of care for patients with rheumatoid arthritis. JAMA 2000;284:984–992.
25. Shekelle PG, Chassin MR, Park RE. Assessing the predictive validity of the RAND/UCLA appropriateness method criteria for performing carotid endarterectomy. Int J Technol Assess Health Care 1998;14:707–727.
26. Kanwal F, Hoang T, Kramer J, et al. Performance of process quality measures in hepatitis C. Am J Gastroenterol 2012. Epub ahead of print.
27. Backus LI, Gavrilov S, Loomis TP, et al. Clinical case registries: simultaneous local and national disease registries for population quality management. J Am Med Inform Assoc 2009;16:775–783.
28. Backus LI, Boothroyd DB, Phillips BR, et al. Predictors of response of US veterans to treatment for the hepatitis C virus. Hepatology 2007;46:37–47.
29. Beste LA, Ioannou GN, Larson MS, et al. Predictors of early treatment discontinuation among patients with genotype 1 hepatitis C and implications for viral eradication. Clin Gastroenterol Hepatol 2010;8:972–978.
30. Kanwal F, Hoang T, Spiegel BM, et al. Predictors of treatment in patients with chronic hepatitis C infection—role of patient versus nonpatient factors. Hepatology 2007;46:1741–1749.
31. Strader DB, Wright T, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39:1147–1171.
32. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002;123:1061–1069.
33. Ferenci P, Fried MW, Shiffman ML, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 kD)/ribavirin. J Hepatol 2005;43:425–433.
34. Centers for Medicare and Medicaid Services. Medicare Quality Measurement and Reporting Programs. Available: http://www.healthreformgps.org/resources/medicare-quality-measurement-and-reporting-programs/. Accessed: March 2012.

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Conflicts of interest

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Supplementary Table 1. Hepatitis C–Specific PMs and Their Operational Definitions

Process-of-care measure	Numerator	Denominator	Rate, % (Number eligible)
Pretreatment domain			
Confirmation of HCV viremia[a]	Patients who received hepatitis C RNA test before or within 12 mo after positive antibody test	Patients with positive hepatitis C antibody test	90.2 (31,193)
Specialty referral	Patients who saw a specialist[b] before or within 12 mo after positive RNA date	Patients with positive hepatitis RNA test	53.6 (34,212)
HCV genotype testing	Patients who received HCV genotype test before or within 12 mo after seeing a specialist	Patients with confirmed viremia who saw a specialist	75.9 (21,640)
Liver biopsy in genotype 1 patients[a]	Patients who received a liver biopsy before or within 12 mo after seeing a specialist	Patients with genotype 1 HCV who saw a specialist	26.3 (13,268)
Autoimmune liver disease testing	Patients who received testing to rule out an autoimmune liver disease before or within 12 mo after seeing a specialist	Patients with confirmed viremia who saw a specialist	53.8 (22,022)
Iron overload testing	Patients who received testing to rule out iron overload before or within 12 mo after seeing a specialist	Patients with confirmed viremia who saw a specialist	71.3 (22,022)
Hepatitis B testing	Patients who received testing to rule out hepatitis B virus co-infection before or within 12 mo after seeing a specialist	Patients with confirmed viremia who saw a specialist	91.2 (22,022)
Preventive and comorbid care domain			
HIV testing[a]	Patients who received an HIV test within 12 mo before or after positive HCV test date	Patients without a previous HIV diagnosis	27.7 (34,265)
Hepatitis A serology testing	Patients who received a hepatitis A serology test within 12 mo after positive HCV test date	Patients with no prior hepatitis A serology test or hepatitis A vaccination	66.5 (32,881)
Hepatitis B serology testing	Patients who received a hepatitis B serology test within 12 mo after positive HCV test date	Patients with no prior hepatitis B serology test or hepatitis B vaccination	81.6 (31,257)
Hepatitis A vaccination	Patients who received at least 1 hepatitis A vaccination[c] within 12 mo after positive HCV test	Patients with no prior hepatitis A vaccination or documented immunity within 1 y after HCV test date	25.1 (26,171)
Hepatitis B vaccination	Patients who received at least 1 hepatitis B vaccination[c] within 12 mo after positive HCV test	Patients with no prior hepatitis B vaccination or documented immunity within 1 y after HCV test date	30.1 (22,863)
Referral for depression management[a]	Patients who received ≥1 of the following treatments for depression: psychotherapy, antidepressant prescription, visit to mental health clinic within 28 d of depression diagnosis	Patients with HCV and a diagnosis of depression[d]	65.6 (13,326)
Referral for SUD	Patients who received ≥1 of the following treatments for SUD: psychotherapy, aversion therapy, visit to mental health clinic within 28 d of SUD diagnosis	Patients with HCV and a diagnosis of SUD[d]	48.7 (18,637)
Treatment monitoring domain			
RNA testing before treatment	Patients who received quantitative RNA test within 6 mo before start of antiviral therapy or 2 wk after	Patients who received their first interferon prescription,[e] and at least 6 mo of follow-up evaluation before interferon start date	69.8 (5588)
RNA testing at treatment week 12	Patients who received RNA test between 10 and 14 wk after start of antiviral therapy	Patients who received their first interferon prescription before 9/24/2006,[e] and at least 12 wk of ongoing treatment[f]	62.3 (4696)

Supplementary Table 1. Continued

Process-of-care measure	Numerator	Denominator	Rate, % (Number eligible)
RNA testing at treatment week 24	Patients who received RNA test between 20 and 28 wk after start of antiviral therapy	Patients who received their first interferon prescription before 6/18/2006,[e] and at least 24 wk of ongoing treatment[f]	62.6 (3427)
RNA testing at treatment week 48	Patients who received RNA test between 44 and 56 wk after start of antiviral therapy	Patients who received their first interferon prescription before 12/4/2005,[e] and at least 48 wk of ongoing treatment[f]	80.3 (1024)
Decreasing ribavirin dose for anemia	Patients who had a dose reduction or discontinuation of ribavirin within 35 d of hemoglobin test date	Patients with hemoglobin level <10 g/dL after first interferon start date and on ribavirin	22.2 (942)
No stimulating factors for low neutrophil count	Patients who did not receive any prescription for colony-stimulating growth factor after the low neutrophil count date	Patients with neutrophil count of 500–700/mm^3 after interferon start date	72.0 (579)

NOTE. For all laboratory tests (SVR HCV antibody, HCV RNA, HCV genotype, hepatitis A and B serology, and HIV), we used Logical Observation Identifiers Names and Codes in combination with laboratory test names to identify relevant tests. We then used laboratory test names and test results to limit to specific tests of interest. For autoimmune liver disease, we used the presence of an antinuclear antibody or smooth muscle antibody test in the laboratory file as evidence that patients received a test for autoimmune liver disease. For iron overload, we determined if a patient received any of the following tests: serum iron, total iron binding capacity, or serum ferritin. For hepatitis B, we used the presence of any of the following hepatitis B serology tests as evidence that the patient received a hepatitis B test: hepatitis B surface antigen, hepatitis B surface antibody, or hepatitis B core antibody. HCV medications were identified using the medication name in the pharmacy data.
HIV, human immunodeficiency virus; SUD, substance use disorder.
[a]Sensitivity analyses: (1) for the confirmation of HCV viremia, we used a broad time frame to allow for variation in clinical practice; some patients might incorrectly receive the antibody test after an RNA test. We opted to give these patients (and their clinicians) the benefit of the doubt if they did not receive another confirmatory test. In a sensitivity analysis, we removed any patient who had the RNA test performed before the HCV antibody test. The rate of confirmatory testing changed from 90.2% to 89.9%. (2) We recalculated the rate of liver biopsy measure by excluding patients with an International Classification of Diseases, 9th revision code for cirrhosis (571.2, 571.5) from the denominator. The rate of liver biopsy measure did not change much before (26.3% [3483 of 13,268]) vs after (26.7% [3310 of 12,417]) implementing this additional criterion. RNA testing at 24 weeks after end of treatment is used to assess SVR. (3) Managing depression in patients who become depressed while on treatment might be important to improve rates of antiviral treatment completion and SVR. Therefore, we reconstructed the depression PMs in those on treatment. We found 545 patients without a prior diagnosis of depression who developed depression while on antiviral treatment. In these patients, 52.3% (285 of 545) received psychotherapy, antidepressant prescription, or had a visit to a mental health clinic within 28 days of a depression diagnosis. (4) We redefined the HIV testing measure by including all patients who received an HIV test any time before or within 1 year of HCV testing. The rate increased from 27.7% to 31% in this analysis. Expanding the time frame for the HIV testing measure to include all HIV tests received by the patient regardless of the time frame increased the rate to 38.9%.
[b]Antiviral treatment is rendered by gastroenterologists (clinic stop code 307), infectious disease (310), and (in some VA facilities) by primary care providers (323). To ascertain which of these 3 clinics served as a specialty clinic for each VA facility, we used pharmacy data and selected the clinic responsible for writing the majority of the first interferon prescriptions for HCV patients in a given facility. We classified a patient as having seen the specialists if she/he had a clinic visit to the specialty clinic, which was accompanied with diagnostic codes for HCV, cirrhosis, or chronic liver disease not specified.
[c]Current Procedural Terminology codes were as follows: hepatitis A vaccination: 90632, 90633, 90634, 90636, and 90730; hepatitis B vaccination: 90636, 90740, 90743, 90744, 90746, 90747, 90748, and G0010. These codes have been reported to be highly predictive of the presence of vaccination in patients' medical records (positive and negative predictive values >90%). (Hachem CY, Kramer JR, Kanwal F, et al. Hepatitis vaccination in patients with hepatitis C: practice and validation of codes at a large Veterans Administration Medical Center. Aliment Pharmacol Ther 2008;28:1078–1087.)
[d]Depression was defined as 1 inpatient or 2 outpatient International Classification of Diseases, 9th revision codes within 1 year.[6] SUD was defined as 1 inpatient visit or outpatient International Classification of Diseases, 9th revision code within 1 year. These included the following: 291.xx, 292.xx, 304.xx, 305.0x, 305.2–305.9, 648.3x, 655.5x, 760.71–760.73, 760.75, 779.5x, 965.0x, 980.0x, V65.42, and 303.xx. In addition, we looked for laboratory evidence of illicit drug use and alcohol use based on blood levels for these agents.
[e]We included only those patients who received the first course of interferon. All patients had >3 months of follow-up evaluation before the first interferon prescription, ensuring that we did not include patients who might have entered the VA while on treatment, thus compromising the ascertainment of the treatment initiation date.
[f]We defined treatment duration by calculating the cumulative days of supply of interferon prescriptions, as previously described by Backus et al.[28] We identified gaps in treatment as the difference between the last date covered by previous prescriptions and the fill date for the next prescription, and classified patients to have received sequential treatment if they had gaps greater than 45 days.

Supplementary Table 2. Association of Process of HCV Care With Antiviral Treatment in Patients Without Treatment Exclusions in the Overall Nationwide Sample and in the Subsample of Patients With Chart Review Data

Process of HCV care	Treatment receipt OR (95% CI)	
	Excluding patients with possible treatment exclusions defined on the basis of clinical and administrative data in the nationwide sample (n = 18,079)	Excluding patients with a documented reason for not receiving treatment in the chart review subsample (n = 231)
Pretreatment care (reference – suboptimum care)	—	—
Optimum care	2.88 (2.57–3.24)	1.84 (0.47–7.19)
Preventive/comorbid care (reference – suboptimum care)	—	—
Optimum care	1.42 (1.21–1.65)	2.38 (0.5–11.38)