RESEARCH

The Effect of Hepatitis C Treatment Response on Medical Costs: A Longitudinal Analysis in an Integrated Care Setting

M. Michele Manos, PhD, MPH, DVM; Jeanne Darbinian, MPH; Jaime Rubin, MPH; G. Thomas Ray, MBA; Valentina Shvachko, MS; Baris Deniz, MSc; Fulton Velez, MD, MSPharm, MBA; and Charles Quesenberry, PhD

ABSTRACT

BACKGROUND: Studies suggest that chronic hepatitis C patients who achieve sustained virologic response (SVR) have lower risks of liver-related morbidity and mortality. Given the substantial costs and complexity of hepatitis C virus (HCV) antiviral treatment, post-treatment benefits are important to understand.

OBJECTIVE: To determine whether health care costs and utilization for up to 5 years after treatment differed between patients who achieved SVR and those who did not.

METHODS: Kaiser Permanente Medical Care Program patients receiving HCV treatment with pegylated interferon and ribavirin (Peg-IFN/RBV) from 2002 to 2007 were retrospectively analyzed, excluding those with human immunodeficiency virus (HIV) or chronic hepatitis B. Health care utilization and costs for up to 5 years after treatment completion were derived from electronic records. We compared mean annual cost and overall post-treatment costs (standardized to year-2007 dollars), and yearly utilization counts between the SVR and non-SVR groups, adjusting for pretreatment costs, age, sex, baseline cirrhosis, and race using gamma and Poisson regression models.

RESULTS: The 1,924 patients eligible for inclusion were a mean age of 50 years; 63% male; 58% white, non-Hispanic; 62% with genotype 1; and 48% who had achieved SVR. The mean duration of post-treatment time was 3 years, and patients without SVR incurred significantly higher health care costs than patients with SVR. For each post-treatment year, total adjusted costs were significantly higher in the non-SVR group than in the SVR group, with rate ratios (RRs) and 95% CIs ranging from 1.26 (95% CI, 1.13-1.40) to 1.64 (95% CI, 1.38-1.96), driven mostly by hospital and outpatient pharmacy costs. When all post-treatment years were considered collectively, the non-SVR group had significantly higher costs overall (RR = 1.41; 95% CI, 1.17-1.69) and in each category of costs. The adjusted difference in yearly total mean costs was $2,648 (95% CI, 737-4,560). In post-treatment years 2-5, adjusted liver-specific laboratory test rates were 1.8 to 2.3 times higher in the non-SVR group than in the SVR group (each year, $P<0.001$). During post-treatment years 1-5, adjusted yearly liver-related hospitalization rates were up to 2.45 times higher (95% CI, 1.56-3.85), and medicine/GI clinic visit rates were up to 1.39 times higher (95% CI, 1.23-1.54) in the non-SVR group compared with the SVR group.

CONCLUSION: Health care utilization and costs after HCV antiviral therapy with Peg-IFN/RBV, particularly for liver-related tests, outpatient drugs, and hospitalizations, were significantly lower for patients who achieved SVR than for those without SVR. Our observations are consistent with the potentially lower risk of severe liver disease among patients with SVR.

J Manag Care Pharm. 2013;19(6):438-47

What is already known about this subject

- Chronic hepatitis C virus (HCV) is the most common bloodborne infection in the United States, affecting approximately 4 million people, most of whom do not know they are infected. Related disease progresses slowly over several decades, and symptoms often go unnoticed until patients develop advanced liver disease, such as decompensated cirrhosis and hepatocellular carcinoma.
- The costs of treating HCV-related complications are expected to rise substantially in the next 5 to 10 years, as the majority of patients will have been infected for more than 2 decades and are at increased risk of developing advanced liver disease.
- Achieving sustained virologic response (SVR) is the primary goal of HCV treatment, and studies suggest that it potentially reduces the risk of advanced liver disease, liver transplant, and liver-related death over the long term. The impact of SVR on resource use and health care costs in the short term has not been fully characterized.

What this study adds

- We conducted a retrospective study of patients receiving treatment with pegylated interferon and ribavirin in the Kaiser Permanente Medical Care Program of Northern California from 2002 to 2007 to quantify the short-term cost and utilization impact of achieving SVR. Using electronic medical records, health care utilization and costs were assessed for up to 5 years after treatment ended. Post-treatment all-cause costs per person per year were $6,301 and $10,149 for the SVR and non-SVR groups, respectively. The adjusted difference in yearly total mean costs was $2,648 (95% CI, 737-4,560).
- When considering costs by post-treatment year, total adjusted costs were significantly higher (up to 1.7 times) in the non-SVR group than in the SVR group, driven mostly by hospital and outpatient pharmacy costs. When all post-treatment years were considered collectively, the non-SVR group had significantly higher costs overall (rate ratio = 1.41; 95% CI, 1.17-1.69) and in each category of costs.
- Non-SVR patients also had higher resource use than did those with SVR, with significantly higher numbers of hospitalizations, liver-specific lab tests, and internal medicine visits in most post-treatment years.

Approximately 4 million people in the United States are chronically infected with hepatitis C virus (HCV).[1-3] Hepatitis C is a slowly progressing disease that is relatively asymptomatic until severe liver disease develops, and at least 50% of the infected population remains undiagnosed in the United States today.[4,5] Despite the often asymptomatic early stages of the condition, chronic hepatitis C can result in liver failure, including decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC).[4,6,7]

A substantial portion of both the economic and health burden of HCV is driven by the development of advanced liver disease (i.e., DCC or HCC).[4] Currently, hepatitis C is the leading cause of HCC and liver transplants in the United States, and studies estimate that liver cirrhosis and HCC will increase 30.5% and 50%, respectively, in the next decade.[3,8-10] Likewise, the health care costs related to HCV were estimated to be $5.46 billion in 1997 and are predicted to increase to $10.7 billion over the next decade.[11,12] Recently published HCV economic analyses estimated that annual total cost per patient was $20,961 for patients with HCV compared with $5,451 in a matched uninfected cohort.[13]

The primary goal of HCV treatment is to prevent morbidity and mortality associated with resultant chronic liver disease. The desired outcome of treatment is sustained virologic response (SVR), defined as undetectable HCV in plasma at least 6 months after the completion of anti-HCV therapy.[14] Based on clinical and laboratory observations, SVR is considered as defining virologic cure.[15,16] Until the spring of 2011, the standard of care for all genotypes of HCV was the combination of pegylated interferon and ribavirin (Peg-IFN/RBV), which leads to SVR in approximately 40% of patients with genotype 1 and 70% to 80% of patients with genotype 2 or 3.[14] Recent studies have shown that SVR is associated with a >80% reduction in complications such as HCC, end-stage liver disease, liver transplant, liver-related death, diabetes, as well as overall mortality.[17-23]

Previous studies that have assessed the economic and clinical value of successful HCV treatment extrapolate the positive impact of SVR on future complications.[24-28] In these studies, an assumption was that virologic cure would provide long-term (i.e., over the course of a person's lifetime) economic and clinical value by reducing future risks of disease-related complications. However, few studies have looked at more immediate long-term cost benefits of SVR. We sought to investigate whether patients who achieved SVR had reduced health care costs compared with those who did not achieve SVR during the period 1 to 5 years after treatment. Specifically, in an integrated managed care setting, we compared the direct medical-care costs and total health care resource utilization up to 5 years following HCV treatment with Peg-IFN/RBV among patients who achieved SVR versus those whose treatment was not successful.

Methods

Setting and Base Population

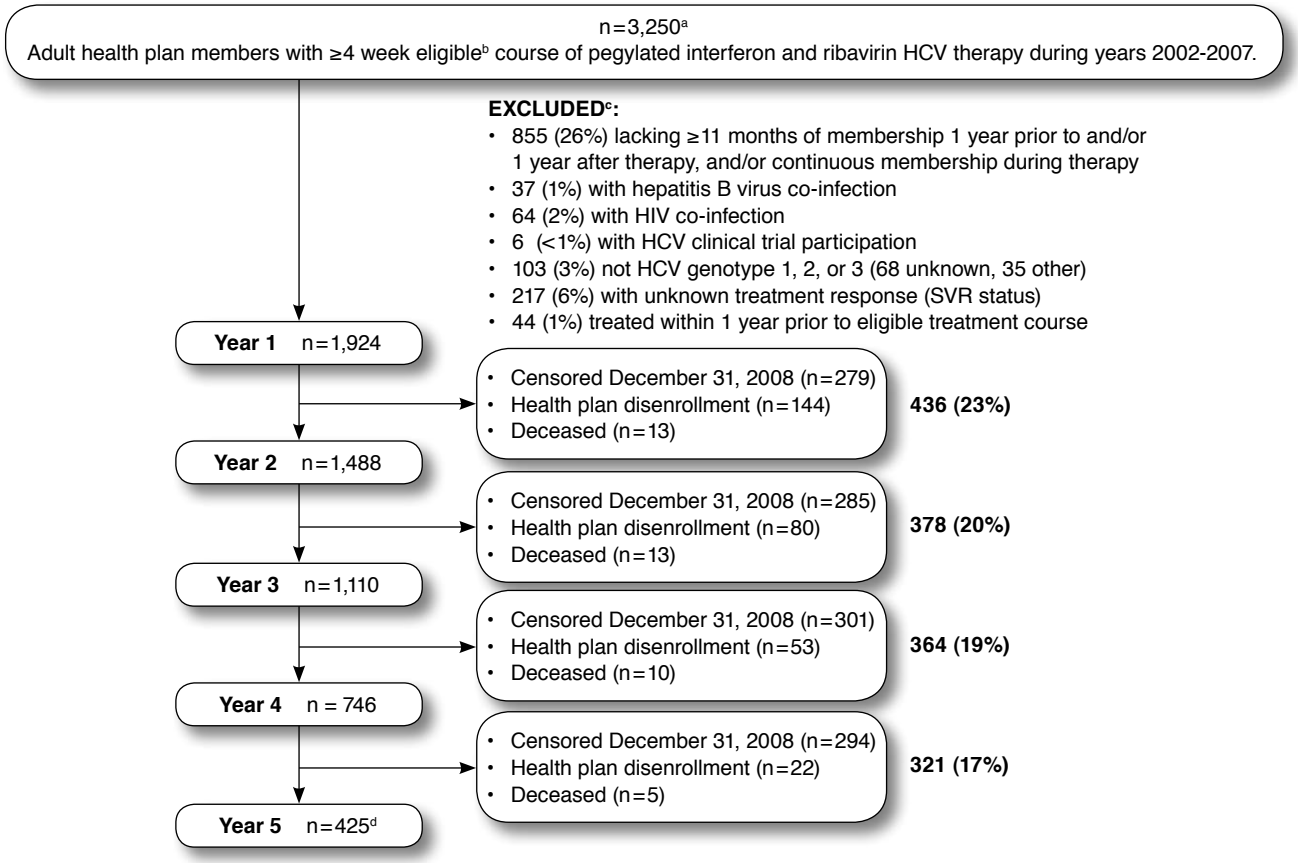
We studied patients who had undergone HCV treatment within the Northern California Kaiser Permanente Medical Care Program (KPNC). The comprehensive, integrated health care delivery system serves more than 3.2 million members in the San Francisco and Sacramento Greater Metropolitan areas. The membership is representative of the area's total insured population except for persons with extremes in income.[29,30] Comprehensive, electronic administrative and clinical data for all KPNC patients with hepatitis C are maintained in the Viral Hepatitis Registry (VHR) and at the time of this investigation included records dated from 1995 through 2008 for 40,307 historical and current patients with hepatitis C. The study protocol was approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

Study Populations

We identified 3,250 adult patients who had undergone a course of at least 4 weeks of Peg-IFN/RBV antiviral therapy for chronic HCV infection between January 1, 2002, and December 31, 2007. We did not include treatment courses defined as pre-transplant (treatment initiation within 18 months prior to a transplant date identified by the KP Transplant Registry database) or treatments occurring after liver transplant. We required at least 11 months of membership in the KPNC health plan for the 1 year prior to treatment initiation and the 1 year after the end of treatment. The end of treatment was defined by the last prescription dispense date plus days of supply. We excluded patients with chronic viral hepatitis B (HBV) and/or human immunodeficiency virus (HIV) co-infection (based on their inclusion in KPNC disease registries), a record of enrollment in an HCV clinical trial, any prior treatment for HCV within the past 12 months, unknown sustained viral response (SVR) status, and HCV genotype unknown or other than 1, 2, or 3. Figure 1 delineates the process. If more than 1 eligible HCV treatment course occurred for a patient during the study period (greater than 12 months apart), we selected the most recent.

For each patient, post-treatment follow-up continued for 1, 2, 3, 4, or 5 years (12-month periods) after the date of ending HCV treatment. Years of eligible follow-up were determined by death, disenrollment from the health plan, or December 31, 2008, whichever occurred first. Inclusion required health plan membership for 11 of the 12 months of that individual's year of follow-up, or death with at least 1 month of membership in that year. For example, an otherwise eligible patient whose treatment ended in December 2007 could contribute only 1 year of follow-up, and a patient whose treatment ended in June of 2006 could contribute only 2 years (the third potential year of follow-up being truncated in December 2008 and being ineligible). A detailed flow diagram of post-treatment attrition of the cohort is shown in Figure 1.

FIGURE 1 *Assembly and Attrition of Study Cohort*



[a]*Identified from 40,307 hepatitis C patients in the KPNC Viral Hepatitis Registry.*
[b]*Does not include treatment courses initiated after or within 18 months prior to liver transplant.*
[c]*Exclusions conducted hierarchically.*
[d]*During the Year 5 period, 8 additional deaths occurred.*
HCV = hepatitis C virus; HIV = human immunodeficiency virus; KPNC = Northern California Kaiser Permanente Medical Care Program; SVR = sustained virologic response.

For patients who died in a follow-up year, utilization and costs up to the time of death were included for that year. This method is based, in part, on the assumption that the patient would have remained a health plan member for the entire year had they not died. We did not adjust cost estimates for time spent alive within that final follow-up year. We chose this approach, to better capture the health care events occurring prior to death, rather than excluding patients from their death year and potentially missing these major costs.

Data Collection

Utilization and cost data were obtained for the period 1 year prior to treatment, during treatment, and all eligible years post-treatment for each patient. Costs for services provided by KPNC were obtained from the Cost Management Information System, an automated system that integrates use and financial databases. Thus, the payer perspective was adopted for the study. Costs, including program and facility overhead, are generated for services using standard accounting methods and program-specific relative value units. From these, we obtained costs of hospitalization and outpatient encounters, including emergency department and office visits as well as radiology and laboratory services. We obtained outpatient pharmacy costs from KPNC's Pharmacy Information Management System, which records information on all prescription drugs dispensed at KPNC outpatient pharmacies. For services covered by KPNC but provided by non-KPNC vendors, we used payments made to those vendors. This study does not include any patient out-of-pocket expenses, and all costs were adjusted to year-2007 dollars using the Consumer Price Index.

We obtained health care utilization data from the KPNC electronic medical record system and other automated databases. These databases capture laboratory tests and results, hospitalizations, emergency department visits, and outpatient clinic visits. Laboratory tests were stratified by whether they were considered liver-disease related (codes for all HCV tests, creatinine, bilirubin, serum albumin, alanine amino transferase, aspartate amino transferase, gamma-glutamyl transferase, alpha-fetoprotein). Diabetes was assigned by whether the patient was included in the KPNC Diabetes Registry.[31] Cirrhosis was defined by evidence on a liver biopsy or a medical record diagnosis (equivalent to *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) codes 571.2, 571.5, 571.6).

Baseline, on-treatment, and response information was obtained from the KPNC VHR databases. SVR status was assigned based on laboratory records and defined as is standard[10]: undetectable viral RNA (lower limit of detection, 7 IU/ml) at 24 weeks or later after the course of treatment.

Different HCV genotypes require distinct antiviral therapy regimens and were grouped to reflect this. Selected findings are presented stratified by the viral genotype groups, making them available for future studies that may consider on-treatment costs or utilization in combination with post-treatment information.

Analyses of Differences in Mean Medical Costs

We obtained estimates of adjusted differences in mean annual post-treatment costs between the non-SVR group and those who attained SVR, using linear regression models in which the dependent variable was cost. We assessed total costs and costs stratified by care setting, including hospital, outpatient pharmacy, and outpatient nonpharmacy. "Hospital costs" included the cost of hospitalizations (including same-day hospitalizations), skilled nursing facility stays, home health care visits, and hospice care. Outpatient nonpharmacy costs included the cost of laboratory and radiology services, emergency department visits, clinic visits, and durable medical equipment.

The primary independent variable was SVR group (comparing those who did not achieve SVR with those who did). We adjusted for age at the end of treatment, race/ethnicity, sex, and history of cirrhosis (prior to start of treatment). We also included total costs incurred during the 1-year period prior to treatment initiation (entered as quintiles) as a proxy for baseline health status and propensity to use services.[32,33] Utility of this proxy was evidenced by the observation that inclusion of it in models ameliorated the substantial effects of pretreatment diabetes or depression.[34] We applied weighting based on total number of post-treatment years in the study and obtained estimates for the entire analytic cohort and for each HCV genotype subset (1 and 2/3).

Analyses of Proportional Differences in Mean Medical Costs

To estimate the proportional differences in post-treatment costs (expressed as rate ratios [RRs]) showing the ratio of the non-SVR group compared with the referent SVR group), we ran separate generalized models under the gamma distribution with log link (i.e., log-linear) for each year of follow-up.[35] For these log-linear gamma models, the dependent variable was the person's direct medical cost in that year and the primary independent variable was SVR group (comparing those who did not achieve SVR with those who did). Because gamma distribution modeling would exclude any records with no costs, we added $1 to each care category of summarized costs in each post-treatment year that an individual cohort member remained in the study.[36,37] This allowed us to retain all eligible records under study (for a given year and care setting of cost). We adjusted for age at the end of treatment, race/ethnicity, sex, history of cirrhosis, and pretreatment costs.

In addition to modeling costs separately for each post-treatment year, we also used log-linear gamma models in which we combined post-treatment costs for all years of follow-up in a series of repeated measures models with estimation via generalized estimating equations (GEE) with an autoregressive covariance structure to account for correlation among different post-treatment years for the same person. We ran these models for the entire cohort and also stratified by HCV genotype (1 versus 2/3). Furthermore, we tested for heterogeneity in the SVR effect over time by including all years for the cohort in a repeated measures model (via GEE) that contained an interaction term of post-treatment year by SVR–non-SVR indicator.

Analyses of Health Services Utilization

To assess differences in health care services use by SVR group, we used Poisson regression, with allowance for over-dispersion (variance > mean) or under-dispersion (variance < mean). The dependent variable was counts of health care services use for each care category assessed (e.g., hospitalizations, outpatient laboratory test results, ambulatory care clinic visits). Liver-related laboratory tests included liver chemistry and any HCV tests. For hospitalizations, we counted admissions that included an overnight stay. The principal predictor was SVR group, adjusting for age at end of treatment, sex, race/ethnicity, history of cirrhosis prior to start of treatment, and quintile of pretreatment costs. As with the cost analysis, we ran separate models for each post-treatment year. We also tested for heterogeneity in the SVR effect over time by including all years in a repeated measures model that contained an interaction term of post-treatment year by SVR status. We used a GEE approach to account for the within-patient correlation in yearly utilization counts.

Results

Characteristics of the Analytic Cohort

The complete analytic cohort consisted of 1,924 patients of whom 63% were male, 58% non-Hispanic white, and 62% had HCV genotype 1. Almost half (48%) had achieved SVR. The mean age at the end of treatment was approximately 50 years; and mean post-treatment (follow-up) time was 3.0 and 2.9 years in the SVR and non-SVR groups, respectively. Table 1 shows characteristics of the total cohort stratified by treatment response group. Numbers of patients eligible for inclusion in analyses decreased by the year of follow-up (Figure 1); in year 5, only 425 patients remained in the study population. Cohort characteristics such as demographics and SVR status were virtually identical in all post-treatment years (not shown).

Post-Treatment Activity

Post-treatment total (all cause) costs per person per year were an average of $8,286 for the entire cohort, and $6,301 and $10,149 for the SVR and non-SVR groups, respectively (Table 2). Compared with those who attained SVR, patients in the non-SVR group incurred higher post-treatment costs in all categories assessed (total, hospital, and outpatient, whether pooled or distinguished as nonpharmacy and pharmacy). During each of the post-treatment years, 85% to 87% of the SVR group had no hospitalizations compared with 73% to 82% of the non-SVR group each year (data not shown).

Table 2 also shows that post-treatment utilization per person-year was higher in the non-SVR compared with the SVR group for the 4 major categories of services studied: hospital stays, liver-related outpatient laboratory tests, other outpatient laboratory tests, and outpatient internal medicine clinic visits (includes gastroenterology and infectious diseases clinics).

Differences in Mean Direct Medical Costs

Table 3 shows the adjusted differences in mean annual costs of the non-SVR group compared with the SVR group. Overall, patients without SVR incurred significantly higher annual post-treatment costs than did those who achieved SVR. This was observed for all categories analyzed, regardless of HCV genotype. Hospital costs did not show significant adjusted differences between the 2 groups. However, outpatient costs overall and by category showed significantly higher costs in the non-SVR group than in the SVR group, again regardless of HCV genotype.

Proportional Differences in Mean Direct Medical Costs

To further evaluate cost differences, we calculated the adjusted RRs of costs of patients in the non-SVR group compared with the SVR group. Adjusted RRs revealed that total costs for the non-SVR group were significantly higher (26%-64%) than those of the SVR group during each of post-treatment years 1 to 5 (Figure 2). For total and hospital costs, the adjusted RR (non-SVR compared with the SVR group) increased from years 1 to 3 post-treatment. By year 4, this increasing trend in cost differences appeared to taper off, although adjusted RR for total costs remained significant and over 1.4. When considering total outpatient post-treatment cost differences (i.e., excluding hospitalizations), the adjusted RRs for the non-SVR versus SVR group ranged by year from 1.18 to 1.34 (all

TABLE 1 Characteristics of the Study Cohort (*n* = 1,924)

	Treatment Response Group			
	SVR (n = 927)	Non-SVR (n = 997)	*P* Value[a]	Total (n = 1,924)
Characteristic	N (%) or Mean ± SD			
Sex				
Female	389 (42.0)	325 (32.6)	< 0.001	714 (37.1)
Male	538 (48.0)	672 (67.4)		1,210 (62.9)
Age at end of therapy (years)				
Mean ± SD	50.0 ± 7.8	50.8 ± 7.0	0.01	50.4 ± 7.4
Median (range)	50 (20-76)	51 (20-76)		50.5 (20-76)
20-49	427 (46.1)	409 (41.0)	0.03	836 (43.4)
50 +	500 (53.9)	588 (59.0)		1,088 (56.6)
Race				
White, non-Hispanic	580 (62.6)	544 (54.6)	< 0.001	1,124 (58.4)
Asian/Pacific Islander	105 (11.3)	78 (7.8)		183 (9.5)
Black	46 (5.0)	125 (12.5)		171 (8.9)
Hispanic	101 (10.9)	163 (16.3)		264 (13.7)
Native American	31 (3.3)	24 (2.4)		55 (2.9)
Unknown	64 (6.9)	63 (6.3)		127 (6.6)
HCV genotype category[b]				
1	399 (43.0)	795 (79.7)	< 0.001	1,194 (62.1)
2	326 (35.2)	99 (9.9)		425 (22.1)
3	202 (21.8)	103 (10.3)		305 (15.8)
SVR status				
SVR				927 (48.2)
Non-SVR				997 (51.8)
Post-treatment follow-up (years)	2.97 ± 1.44	2.94 ± 1.49	0.66	2.96 ± 1.47
Diabetes[c]	71 (7.7)	155 (15.5)	< 0.001	226 (11.8)
History of cirrhosis[c]	54 (5.8)	149 (14.9)	< 0.001	203 (10.6)
Quintile of pretreatment costs ($)[d]				
1	195 (21.0)	189 (19.0)	0.397	384 (20.0)
2	190 (20.5)	195 (19.6)		385 (20.0)
3	192 (20.7)	193 (19.4)		385 (20.0)
4	177 (19.1)	208 (20.9)		385 (20.0)
5	173 (18.7)	212 (21.3)		385 (20.0)

[a] *P values for chi-square statistic (categorical data) and t-test for continuous measures.*

[b] *Most recent to treatment start.*

[c] *Prior to treatment.*

[d] *Cut-points for quintile of pretreatment costs ($) — quintile 1: ≤ 2,561; 2: 2,562-3,788; 3: 3,789-5,235; 4: 5,236-8,481; 5: ≥ 8,482.*

HCV = hepatitis C virus; SD = standard deviation; SVR = sustained virologic response.

TABLE 2 Mean Post-Treatment Costs and Utilization

Category of Cost or Utilization	Treatment Response Group		
	SVR (n = 927)	Non-SVR (n = 997)	Total (n = 1,924)
	Mean (95% CI)[b]		
Costs per person-year ($)[a]			
Total	6,301 (5,615-7,215)	10,149 (8,918-11,492)	8,286 (7,572-9,092)
Hospital	2,641 (2,035-3,459)	5,167 (4,035-6,395)	3,944 (3,281-4,699)
Outpatient	3,661 (3,479-3,854)	4,983 (4,716-5,279)	4,343 (4,183-4,519)
Nonpharmacy	2,954 (2,796-3,122)	3,947 (3,736-4,180)	3,466 (3,334-3,610)
Pharmacy	708 (654-764)	1,037 (948-1,132)	878 (823-935)
Utilization per person-year[c]			
Hospitalizations	0.09 (0.08-0.11)	0.16 (0.14-0.19)	0.13 (0.11-0.14)
Liver-related labs	7.6 (7.3-8.0)	11.8 (11.3-12.5)	9.8 (9.5-10.2)
Other labs	41.6 (39.4-44.1)	60 (56.9-63.4)	51.1 (49.2-53.1)
Internal medicine clinic visits	4.5 (4.3-4.7)	5.8 (5.5-6.0)	5.2 (5.0-5.3)

[a]*Per person-year costs adjusted to year 2007 dollars using Consumer Price Index.*
[b]*Sample mean shown with bootstrapped 95% CIs.*
[c]*Based on total counts (e.g., laboratory test results, hospital admissions, office visits).*
CI = confidence interval; SVR = sustained virologic response.

$P < 0.03$; see Appendix A, available online). The differences in outpatient costs, while still statistically significant, appeared to plateau by year 2 and then taper off by years 4-5. Based on the adjusted RR for nonpharmacy outpatient costs, the non-SVR group incurred significantly higher costs in this category than did the SVR group during post-treatment years 1-3 (Figure 2). For outpatient pharmacy costs, significant adjusted RRs were found for each year (ranging from 1.2 to 1.8 by year) for the non-SVR group compared with those who achieved SVR. While we observed no statistically significant differences over time in the SVR effect within any cost category, an increasing trend for outpatient pharmacy was evident ($P = 0.26$; Figure 2).

Table 4 shows the adjusted RRs for mean annual costs (all years combined) for the full cohort and stratified by HCV genotype (1 versus 2/3). In summary, compared with those who attained SVR, adjusted total, hospital, and outpatient costs for patients in the non-SVR group were 1.4, 1.7, and 1.4 times higher, respectively (all $P < 0.01$). We observed similar and significant patterns for patients in both HCV genotype groups although the differences were somewhat more pronounced for patients with genotype 2/3 (versus 1).

TABLE 3 Differences in Mean Post-Treatment Costs: Non-SVR Group Versus SVR Group[a]

Category of Costs	Total Cohort (n = 1,924)		HCV Genotype 1 (n = 1,194)		HCV Genotype 2/3 (n = 730)	
	Adjusted Difference in Mean Costs ($) (95% CI)	*P* Value	Adjusted Difference in Mean Costs ($) (95% CI)	*P* Value	Adjusted Difference in Mean Costs ($) (95% CI)	*P* Value
Total	2,648 (737-4,560)	0.007	2,504 (89-4,920)	0.042	3,904 (91-7,717)	0.045
Hospital	1,599 (-125-3,324)	0.069	1,522 (-654-3,699)	0.170	2,499 (-953-5,951)	0.156
Outpatient	1,049 (610-1,488)	< 0.001	982 (376-1,588)	0.002	1,405 (645-2,165)	< 0.001
Nonpharmacy	752 (388-1,116)	< 0.001	699 (180-1,218)	0.008	906 (318-1,495)	0.002
Pharmacy	297 (150-444)	< 0.001	283 (100-467)	0.003	499 (203-795)	0.001

[a]*Difference in yearly costs ($) of non-SVR group versus patients with SVR. Adjusted for age, sex, race/ethnicity, cirrhosis history, pretreatment costs. Weighted regression, based on total number of post-treatment years in study.*
CI = confidence interval; HCV = hepatitis C virus; SVR = sustained virologic response.

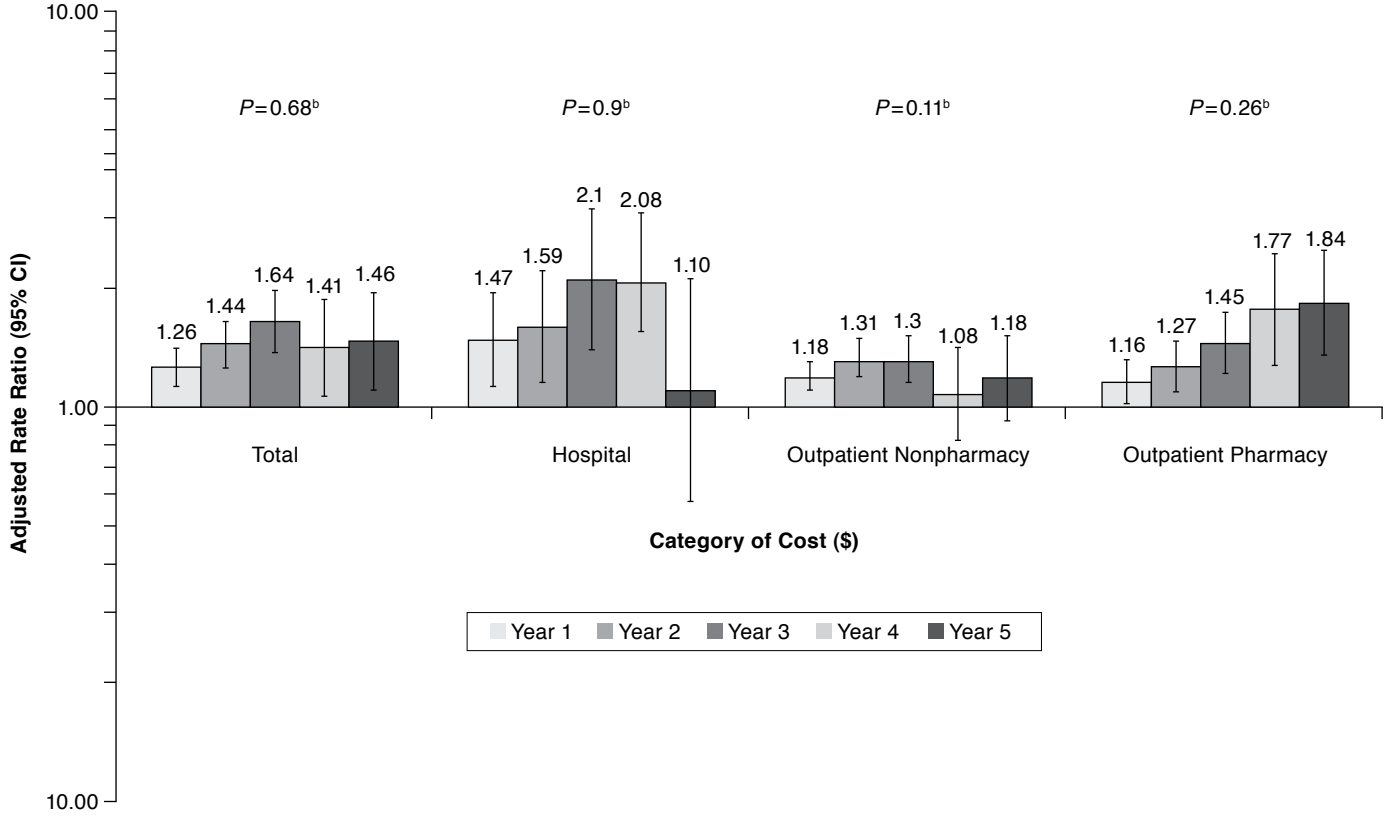
Post-Treatment Health Services Utilization

We sought to further understand the observed cost differences between patients with and without SVR by comparing selected health care utilization in the post-treatment period. Figure 3 shows results from Poisson regression models comparing relative utilization rates of the non-SVR group compared with the SVR groups, adjusting for key factors. In post-treatment years 2-5, overall (not shown) and liver-specific laboratory test rates were approximately 60% to 80% and 70% to 130% higher, respectively, in the non-SVR group compared with those who attained SVR ($P < 0.001$ for each year of follow-up time). Internal medicine (including gastroenterology and infectious diseases) clinic visit rates were 20% to 40% higher in the non-SVR group compared with SVR patients in years 2-5 after treatment ($P < 0.001$ for those years). Hospitalization rates fluctuated by post-treatment year from 10% to 145% higher in the non-SVR group compared with SVR patients. There were statistically significant differences in SVR effect over time for liver-related lab tests, other lab tests, and internal medicine outpatient visits. In particular, there was a strong increasing trend in adjusted RR for liver-related lab tests (see Appendix B, available online).

Discussion

This study found that health care utilization rates and direct medical costs up to 5 years after HCV antiviral therapy were significantly higher among patients who did not achieve SVR than among those achieving viral clearance. Rates of hospitalization following treatment completion were higher among non-SVR patients than those with SVR, although small numbers

FIGURE 2 Rate Ratios for Incurred Costs by Post-Treatment Year: Non-SVR Group Compared with SVR Group[a]



[a]*Rate ratios of non-SVR group relative to SVR group graphed on logarithmic scale. Values above each bar represent the rate ratio. Bars represent 95% CIs.*
[b]*P values for test of heterogeneity over time in association between SVR and costs.*
CI = confidence interval; SVR = sustained virologic response.

of events were recorded in both groups. Over a 5-year period, health care costs and utilization for some care categories suggest that differences (expressed as RRs) between the SVR and non-SVR groups increase in the first 2-3 years and then plateau or decrease. However, point estimates in all years indicated higher cost and resource use overall in patients not achieving SVR compared with those with SVR. Particularly, significantly increasing differences in liver-related tests and outpatient pharmacy costs over the 5-year period were observed when comparing the 2 SVR groups. We found significantly higher costs and utilization among patients without SVR compared with SVR patients regardless of HCV genotype. The effect of SVR (based on adjusted differences in mean annual cost and on adjusted risk ratios) appeared somewhat stronger in the genotype 2/3 group than among those with genotype 1. However, there were no significant differences between the estimates in the 2 genotype groups, and the genotype 2/3 afforded less precise estimates due to the smaller numbers of patients.

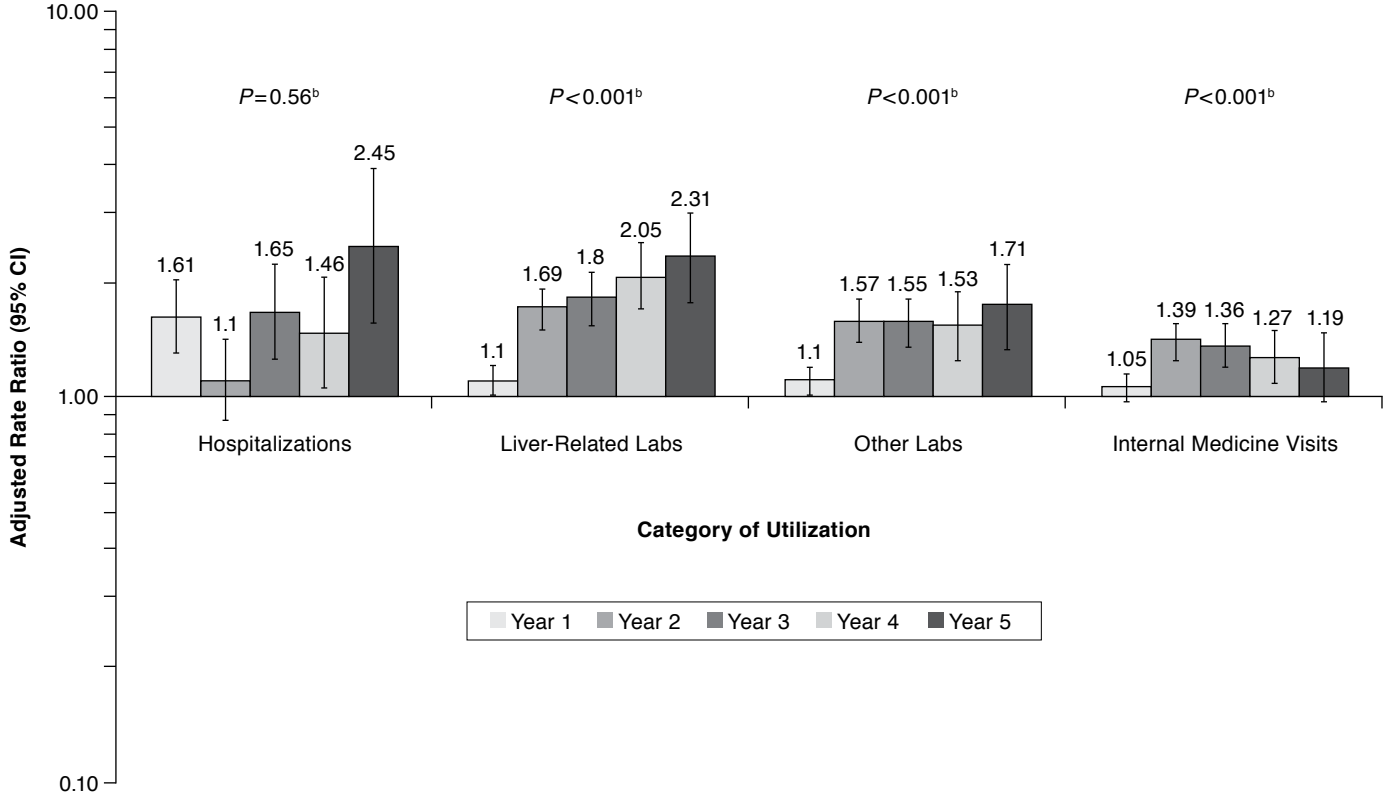
While directly comparable studies are not available in the literature, our findings are consistent with prior observations

TABLE 4 Post-Treatment Costs Incurred: Rate Ratios[a] for Non-SVR Versus SVR Group

	Total Cohort		HCV Genotype			
	(n=1,924)		1 (n = 1,194)		2/3 (n = 730)	
Category of Costs	Adjusted Rate Ratio (95% CI)	*P* Value	Adjusted Rate Ratio (95% CI)	*P* Value	Adjusted Rate Ratio (95% CI)	*P* Value
Total	1.41 (1.17-1.69)	<0.001	1.30 (1.11-1.54)	0.010	1.65 (1.14-2.38)	0.007
Hospital	1.66 (1.18-2.34)	<0.001	1.41 (1.01-1.97)	0.045	2.34 (1.23-4.43)	0.009
Outpatient	1.41 (1.09-1.82)	0.009	1.21 (1.08-1.35)	0.004	1.39 (1.16-1.67)	<0.001
Nonpharmacy	1.26 (1.16-1.37)	<0.001	1.20 (1.07-1.33)	0.008	1.31 (1.11-1.55)	0.002
Pharmacy	1.39 (1.16-1.66)	<0.001	1.29 (1.07-1.55)	0.012	1.68 (1.15-2.46)	0.008

[a]*Adjusted for age, sex, race/ethnicity, cirrhosis history, pretreatment costs. Modeled as repeated measures using generalized estimating equations (GEE): log-linear models under gamma distribution.*
CI = confidence interval; HCV = hepatitis C virus; SVR = sustained virologic response.

FIGURE 3 Rate Ratios for Health Care Utilization by Post-Treatment Year: Non-SVR Group Compared with SVR Group[a]



[a]*Rate ratios of non-SVR group relative to SVR group graphed on logarithmic scale. Values above each bar represent the rate ratio. Bars represent 95% CIs.*
[b]*P values for test of heterogeneity over time in association between SVR and utilization counts.*
CI = confidence interval; SVR = sustained virologic response.

about disease progression and health care costs of patients with hepatitis C. Certainly, the cost of hepatitis patient care increases as liver disease severity progresses. Given that SVR serves to slow HCV-associated disease progression, our findings of lower post-treatment health care costs and utilization are both plausible and predictable.

A recent study compared health care costs among treated hepatitis C patients with and without SVR in the 6 months immediately following the end of treatment.[13] They reported that patients not achieving SVR incurred about twice the total monthly costs of those with SVR ($717 vs. $1,436; $P < 0.001$); the differences were largely attributable to hospital costs. While the general conclusions are consistent with our findings, the results of Davis et al. suggest a more marked difference in costs between the 2 groups in the first year after treatment than we found. The small number but large relative contribution to costs of hospitalizations in both studies limits a useful comparison. Davis et al. reported no significant differences in office visits, other outpatient services, or laboratory tests during the immediate post-treatment period studied. This is consistent with our findings of the smallest differences in health care costs between SVR groups in the first year post-treatment. Regardless of response status, patients may be tested and managed for lingering treatment side effects (e.g. anemia, depression) in the months following treatment. Patients with undetectable HCV at the end of treatment, most of whom will be defined as SVR, are being seen for response-defining HCV RNA testing 24 weeks later.

With the advent of novel HCV antivirals with higher SVR rates compared with older therapies, and higher costs, it is important to contextualize the benefits of SVR when evaluating cost-effectiveness. Due to the typically slow progression of liver disease among the portion of patients developing complications from HCV infection, the estimated cost-effectiveness for HCV treatment may improve with increasing length of post-treatment time. Despite such projected longer term benefits of therapy,[13,26,38] payers may consider the value of therapies primarily in the short term, consistent with 1- to 2-year budget

timelines. SVR appears to confer shorter-term economic benefits such as reductions in health care resource use for managing and monitoring HCV infection.

Limitations

We did not include never-infected control or untreated hepatitis C patients, and thus did not address the health care utilization or costs in those groups. Our study focused on all-cause costs and utilization; we did not attempt to distinguish events specifically related to liver health. However, since the study was limited to patients treated for hepatitis C and we used adjustment for utilization (through costs) prior to treatment, we believe the cost differences and RRs are reflective of the effects of viral clearance in this population. Certainly some factors affecting liver disease progression (and associated utilization and cost) are also predictors of SVR. Our models control for the major factor, baseline cirrhosis, as well as demographic factors such as age and sex. Additionally, comorbid conditions such as diabetes are accounted for, at least in part, by the adjustment for pretreatment cost. Of course, some confounding by predictors of SVR may still be present in the findings, but we posit that this is minimal.

Although our study was conducted retrospectively, its reliance on comprehensive electronic records allowed for complete assessment of a large number of patients, thus giving increased precision to our point estimates. Negligible, if any, misclassification of treatment response status is suspected since laboratory records and strict definitions of SVR were used. In addition, individuals with unknown SVR status (n = 200) were excluded; how these patients might differ from those included and how their exclusion impacted the results is unknown. Importantly though, the design remains subject to confounding by factors that influence the likelihood of SVR. Many such factors (race, cirrhosis, sex, age) were adjusted for in the models, minimizing bias related to these characteristics. However, factors not observable in the database such as drug and alcohol use or socioeconomic factors may have introduced some bias in results.

As expected with this study design in a health plan membership population, attrition of the study cohort occurred. The majority of attrition was due to maximal follow-up at December 31, 2008, leading to incremental reductions in sample size over the 5-year follow-up period (Figure 1). Just 16% of patients were lost to follow-up due to disenrollment from the health plan, ranging from 3% to 7% per follow-up year. Because the distributions of patient characteristics considered were similar in the cohorts over time, we believe that there are no systematic differences introduced by the attrition.

Although few patients were hospitalized in this study, hospital stays were a major contributor to cost and to the differentiation of costs between SVR and non-SVR patients. The low number of hospital events, and the high variance in the cost of such events, contributes to the imprecision of hospitalization rate and cost estimates. Hospitalization rates and costs were driven by events occurring among just 20% of the cohort. Furthermore, the most expensive outlier costs overall were attributable to hospitalizations. In absolute terms, the post-treatment rate of hospital admissions for the SVR cohort was 0.09 per person per year versus 0.16 among those not achieving SVR (unadjusted RR = 1.75; $P < 0.001$). However, these numbers should be considered in the context of the small number of events. Nonhospital costs offer more robust comparisons, given that almost every cohort member (98%) had such costs in each post-treatment year. We did find significantly higher adjusted total outpatient costs in the non-SVR group (versus the SVR group) in each post-treatment year.

Conclusion

Our study suggests that among patients treated for hepatitis C, SVR may be associated with significant reductions in future health care resource use and costs. Specifically, the findings reveal economic benefits of SVR within the first 5 years after treatment. Additionally, selected findings may be applied to other settings to estimate the potential impact of the successful treatment of hepatitis C on subsequent health care costs and utilization.

Authors

M. MICHELE MANOS, PhD, MPH, DVM, is Senior Investigator and Director, Viral Hepatitis Registry; JEANNE DARBINIAN, MPH, is Data Consultant; G. THOMAS RAY, MBA, is Senior Data Consultant; VALENTINA SHVACHKO, MS, is Data Consultant; and CHARLES QUESENBERRY, PhD, is Senior Biostatistician, Kaiser Permanente Division of Research, Oakland, California. JAIME RUBIN, MPH, is Associate Director; BARIS DENIZ, MSc, was Associate Director; and FULTON VELEZ, MD, MSPharm, MBA, was Manager, Health Economics, Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts.

AUTHOR CORRESPONDENCE: M. Michele Manos, PhD, MPH, DVM, Senior Investigator and Director, Viral Hepatitis Registry, 2000 Broadway, Oakland, CA 94612-2304. Tel.: 510.891.3464; Cell: 510.928.2348; Fax: 510.891.3802; E-mail: michele.manos@kp.org.

DISCLOSURES

This study was funded by Vertex Pharmaceuticals Incorporated. Manos, Darbinian, and Shvachko report that they have received grants from Vertex, Merck, Roche, and Gilead; Ray reports that he has received grants from Vertex, Pfizer, Merck, GlaxoSmithKline, and Purdue; and Quesenberry reports that he has not received any funding. The other authors have not disclosed any funding related to this article other than from Vertex Pharmaceuticals.

Study concept and design were contributed primarily by Manos, with assistance from Quesenberry, Deniz, Ray, Darbinian, and Velez. Darbinian had primary responsibility for data collection, with assistance from Shvachko; data interpretation was the work of Manos, Quesenberry, Ray, Darbinian, Deniz, and Rubin. The manuscript was written primarily by Manos, with assistance from Darbinian and input from Quesenberry, Rubin, and Deniz and was revised primarily by Manos with input from Quesenberry, Ray, Darbinian, and Rubin.

ACKNOWLEDGMENTS

We thank Rosemary Murphy for help with tables and graphics and Bruce Fireman for helpful discussions.

REFERENCES

1. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med.* 1999;341(8):556-62.

2. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006;144(10):705-14.

3. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010;138(2):513-21.

4. Colvin HM, Mitchell AE, eds. Committee on the Prevention and Control of Viral Hepatitis Infections, Institute of Medicine. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C.* Washington, DC: The National Academies Press; 2010:4.

5. Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR.* 2012;61(RR04):1-32.

6. Jacobson IM, Davis GL, El-Serag H, Negro F, Trepo C. Prevalence and challenges of liver diseases in patients with chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol.* 2010;8(11):924-33; quiz e117.

7. McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. *J Manag Care Pharm.* 2011;17(7):531-46.

8. Di Bisceglie AM, Lyra AC, Schwartz M, et al. Hepatitis C-related hepatocellular carcinoma in the United States: influence of ethnic status. *Am J Gastroenterol.* 2003;98(9):2060-63.

9. HHS. 2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. Available at: http://optn.transplant.hrsa.gov/ar2009/. Accessed April 24, 2013.

10. NIH. Management of hepatitis C. Paper presented at: National Institutes of Health Consensus Conference; June 10-12, 2002; Bethesda, MD.

11. Leigh JP, Bowlus CL, Leistikow BN, Schenker M. Costs of hepatitis C. *Arch Intern Med.* 2001;161(18):2231-37.

12. Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health.* 2000;90(10):1562-69.

13. Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. *J Clin Gastroenterol.* 2011;45(2):e17-24.

14. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49(4):1335-74.

15. Fujiwara K, Allison RD, Wang RY, et al. Investigation of residual hepatitis C virus in presumed recovered subjects. *Hepatology.* 2013;57(2):483-91.

16. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology.* 2010;139(5):1593-601.

17. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology.* 2010;52(3):833-44.

18. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol.* 2011;9(6):509-16, e501.

19. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology.* 2007;45(3):579-87.

20. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med.* 2007;147(10):677-84.

21. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol.* 2010;8(3):280-88.

22. Manos MM, Zhao W, Shvachko VA. HCV-genotype-specific influences on incident diabetes: the effect of sustained viral response to antiviral therapy. *Hepatology.* 2009;50(4):358A.

23. Arase Y, Suzuki F, Suzuki Y, et al. Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. *Hepatology.* 2009;49(3):739-44.

24. Campos NG, Salomon JA, Servoss JC, et al. Cost-effectiveness of treatment for hepatitis C in an urban cohort co-infected with HIV. *Am J Med.* 2007;120(3):272-79.

25. Malone DC, Tran TT, Poordad FF. Cost-efficacy analysis of peginterferon alfa-2b plus ribavirin compared with peginterferon alfa-2a plus ribavirin for the treatment of chronic hepatitis C. *J Manag Care Pharm.* 2005;11(8):687-94.

26. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *JAMA.* 2003;290(2):228-37.

27. Wong JB. Hepatitis C: cost of illness and considerations for the economic evaluation of antiviral therapies. *Pharmacoeconomics.* 2006;24(7):661-72.

28. Solomon M, Bonafede M, Pan K, et al. Direct medical care costs among pegylated interferon plus ribavirin-treated and untreated chronic hepatitis C patients. *Dig Dis Sci.* 2011;56(10):3024-31.

29. Gordon N. Similarity of the adult Kaiser Permanente membership in northern California to the insured and general population in northern California: statistics from the 2007 California Health Interview Survey. Internal Report: Kaiser Permanente Division of Research; 2012.

30. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health.* 1992;82(5):703-10.

31. Karter AJ, Schillinger D, Adams AS, et al. Elevated rates of diabetes in Pacific Islanders and Asian subgroups: the Diabetes Study of Northern California (DISTANCE). *Diabetes Care.* 2013;36(3):574-79.

32. Otani K, Baden WW. Healthcare cost and predictive factors: high- and low-utilization model development. *Health Mark Q.* 2009;26(3):198-208.

33. Meenan RT, Goodman MJ, Fishman PA, Hornbrook MC, O'Keeffe-Rosetti MC, Bachman DJ. Using risk-adjustment models to identify high-cost risks. *Med Care.* 2003;41(11):1301-12.

34. Welch CA, Czerwinski D, Ghimire B, Bertsimas D. Depression and costs of health care. *Psychosomatics.* 2009;50(4):392-401.

35. Dodd S, Bassi A, Bodger K, Williamson P. A comparison of multivariable regression models to analyse cost data. *J Eval Clin Pract.* 2006;12(1):76-86.

36. Skrepnek GH. Regression methods in the empiric analysis of health care data. *J Manag Care Pharm.* 2005;11(3):240-51.

37. Diehr P, Yanez D, Ash A, Hornbrook M, Lin DY. Methods for analyzing health care utilization and costs. *Annu Rev Public Health.* 1999;20:125-44.

38. Gerkens S, Nechelput M, Annemans L, et al. A health economic model to assess the cost-effectiveness of PEG IFN alpha-2a and ribavirin in patients with mild chronic hepatitis C. *J Viral Hepat.* 2007;14(8):523-36.

APPENDIX A Adjusted Rate Ratios of Costs Incurred, Non-SVR Compared with SVR Group, by Year Post-Treatment[a]

Category of Costs	Post-Treatment Year	N	Adjusted Rate Ratio, non-SVR vs. SVR (95% CI)	*P* Value	*P* Value for Test of Heterogeneity Over Time
Total	1	1,924	1.26 (1.13-1.40)	<0.001	0.685
	2	1,488	1.44 (1.25-1.65)	<0.001	
	3	1,110	1.64 (1.38-1.96)	<0.001	
	4	746	1.41 (1.14-1.73)	<0.001	
	5	425	1.46 (1.11-1.93)	0.007	
Hospital	1	1,924	1.47 (1.12-1.94)	0.006	0.900
	2	1,488	1.59 (1.14-2.21)	0.007	
	3	1,110	2.10 (1.39-3.18)	<0.001	
	4	746	2.08 (1.28-3.38)	0.003	
	5	425	1.10 (0.57-2.11)	0.781	
Outpatient	1	1,924	1.18 (1.09-1.28)	<0.001	0.089
	2	1,488	1.31 (1.17-1.46)	<0.001	
	3	1,110	1.34 (1.17-1.52)	<0.001	
	4	746	1.21 (1.02-1.43)	0.029	
	5	425	1.28 (1.03-1.60)	0.028	
Nonpharmacy	1	1,924	1.18 (1.09-1.28)	<0.001	0.113
	2	1,488	1.31 (1.17-1.48)	<0.001	
	3	1,110	1.30 (1.13-1.50)	<0.001	
	4	746	1.08 (0.91-1.29)	0.380	
	5	425	1.18 (0.92-1.50)	0.191	
Pharmacy	1	1,924	1.16 (1.02-1.31)	0.022	0.257
	2	1,488	1.27 (1.09-1.47)	0.002	
	3	1,110	1.45 (1.22-1.74)	<0.001	
	4	746	1.77 (1.41-2.22)	<0.001	
	5	425	1.84 (1.35-2.49)	<0.001	

[a]*These data are the basis for Figure 2. Log-linear models under gamma distribution. Adjusted for age at end of treatment, sex, race/ethnicity, history of cirrhosis prior to start of treatment, and quintile of pretreatment costs. P value from time (year post-treatment) x SVR group interaction term, repeated measures/GEE models using gamma distribution.*

CI = confidence interval; GEE = generalized estimating equations; SVR = sustained virologic response.

APPENDIX B Adjusted Rate Ratios for Health Care Utilization, Non-SVR Compared with SVR Group, by Year Post-Treatment[a]

Category of Utilization	Post-Treatment Year	N	Adjusted Rate Ratio, non-SVR vs. SVR (95% CI)	*P* Value	*P* Value for Test of Heterogeneity Over Time
Outpatient lab tests					
All	1	1,924	1.10 (1.02-1.19)	0.013	<0.001
	2	1,488	1.59 (1.42-1.78)	<0.001	
	3	1,110	1.58 (1.37-1.83)	<0.001	
	4	746	1.59 (1.31-1.93)	<0.001	
	5	425	1.78 (1.41-2.26)	<0.001	
Liver-related	1	1,924	1.10 (1.03-1.19)	0.006	<0.001
	2	1,488	1.69 (1.51-1.88)	<0.001	
	3	1,110	1.80 (1.55-2.09)	<0.001	
	4	746	2.05 (1.70-2.48)	<0.001	
	5	425	2.31 (1.79-2.98)	<0.001	
Other lab tests	1	1,924	1.10 (1.01-1.19)	0.020	<0.001
	2	1,488	1.57 (1.40-1.77)	<0.001	
	3	1,110	1.55 (1.34-1.79)	<0.001	
	4	746	1.53 (1.25-1.85)	<0.001	
	5	425	1.71 (1.35-2.17)	<0.001	
Hospitalizations (# admissions)					
	1	1,924	1.61 (1.29-2.02)	<0.001	0.565
	2	1,488	1.10 (0.87-1.40)	0.431	
	3	1,110	1.65 (1.25-2.18)	<0.001	
	4	746	1.46 (1.05-2.03)	0.025	
	5	425	2.45 (1.56-3.85)	<0.001	
Outpatient encounter (# visits)					
Internal medicine	1	1,924	1.05 (0.97-1.13)	0.200	<0.001
	2	1,488	1.39 (1.25-1.54)	<0.001	
	3	1,110	1.36 (1.20-1.54)	<0.001	
	4	746	1.27 (1.09-1.49)	0.003	
	5	425	1.19 (0.98-1.45)	0.079	

[a]*These data are the basis for Figure 3. Adjusted for age at end of treatment, sex, race/ethnicity, total costs one year prior to start of anti-viral therapy (modeled as quintiles), and history of cirrhosis prior to starting treatment. P value from time (year post-treatment) x SVR group interaction term, repeated measures/GEE models using Poisson distribution and scaling for over-dispersion of data.*

CI = confidence interval; GEE = generalized estimating equations; SVR = sustained virologic response.