CLINICAL RESEARCH STUDY

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Telemedicine Specialty Support Promotes Hepatitis C Treatment by Primary Care Providers in the Department of Veterans Affairs

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ABSTRACT

BACKGROUND: The Department of Veterans Affairs is the largest US provider of hepatitis C treatment. Although antiviral regimens are becoming simpler, hepatitis C antivirals are not typically prescribed by primary care providers. The Veterans Affairs Extension for Community Health Outcomes (VA-ECHO) program was launched to promote primary care–based hepatitis C treatment using videoconferencing-based specialist support. We aimed to assess whether primary care provider participation in VA-ECHO was associated with hepatitis C treatment and sustained virologic response.

METHODS: We identified 4173 primary care providers (n = 152 sites) responsible for 38,753 patients with chronic hepatitis C infection. A total of 6431 patients had a primary care provider participating in VA-ECHO; 32,322 patients had an unexposed primary care provider. Exposure was modeled as a patient-level time-varying covariate. Patients became exposed after primary care provider participation in ≥1 VA-ECHO session. Multivariable Cox proportional hazards frailty modeling assessed the association between VA-ECHO exposure and hepatitis C treatment. Among treated patients, modified Poisson regression assessed the relationship between exposure and sustained virologic response.

RESULTS: After adjustment, exposed patients received significantly higher rates of antiviral treatment compared with unexposed patients (adjusted hazard ratio, 1.20; 95% confidence interval, 1.10-1.32; $P < .01$). The rate of primary care provider–initiated antiviral medication was 21.4% among treated patients reviewed on VA-ECHO teleconferences compared with 2.5% among unexposed patients ($P < .01$). No difference in adjusted rates of sustained virologic response was observed for patients with exposed primary care providers ($P = .32$), with similar crude rates for primary care providers versus specialists.

CONCLUSIONS: National implementation of VA-ECHO was positively associated with hepatitis C treatment initiation by primary care providers, without differences in sustained virologic response.

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Hepatitis C virus is a leading cause of cirrhosis and hepatocellular carcinoma. The Department of Veterans Affairs (VA) is the largest integrated healthcare system in the United States and includes the nation's largest cohort of hepatitis C–infected patients.[1] VA users have approximately 3-fold higher rates of chronic hepatitis C compared with the general US population.[2] Although hepatitis C treatment rates in the VA substantially exceed the private sector, approximately 120,000 patients were awaiting antiviral treatment as of late 2015, of whom more than 20% had known or suspected cirrhosis (Backus et al., 2015; personal communication).[2] Without improvement in the rate of antiviral treatment in the United States, hepatitis C complications are expected to accelerate as the population with the highest disease burden—the 1945-1965 birth cohort—accumulates hepatic injury.[3,4]

Although potent oral regimens have simplified hepatitis C treatment, prescribing them predominantly occurs in subspecialty rather than general medical settings. This may be due to health insurer or network requirements[5] or to provider preference. The de facto restriction of hepatitis C treatment to specialists creates potential barriers for patients living in rural or underserved areas, as shown for other conditions.[6-10]

Although most US specialists are concentrated in tertiary centers, an estimated 37.9% of VA users are rural or highly rural. Only half of Veterans designated by the VA as "highly rural" live within 1 hour of primary care, and 70% must travel >4 hours to tertiary care.[11] It remains unknown whether specialty videoconferencing support for primary care providers can affect hepatitis C treatment delivery on a large scale. A single-site study of the longitudinal telemedicine model, Extension of Community Healthcare Outcomes (Project ECHO), found that hepatitis C treatment by primary care providers produces similar outcomes as specialists.[12]

In 2011, the VA became the first US health care system to introduce the ECHO model nationally. The VA Extension of Community Healthcare Outcomes (VA-ECHO) was rolled out across 31 states for a range of specialties and diseases, including hepatitis C.[13] We report the impact of the VA-ECHO program on national rates of hepatitis C treatment initiation and sustained virologic response.

CLINICAL SIGNIFICANCE

- A structured telementorship program offered by hepatitis C specialists to primary care providers was associated with increased rates of primary care provider–initiated hepatitis C treatment in the national Veterans Affairs healthcare system.
- Exposure to telementorship was positively associated with rates of hepatitis C virus treatment initiation, with equivalent outcomes among treated patients.
- National implementation of telementorship has the potential to increase the uptake of hepatitis C virus treatment delivery in primary care.

MATERIALS AND METHODS

Veterans Affairs Extension of Community Healthcare Outcomes Program

The VA healthcare system includes 21 regions, 152 medical centers, 875 ambulatory clinics, and 35 domiciliary facilities. VA-ECHO was gradually rolled out starting in April 2011 to 152 of 952 primary care sites nationwide.[13,14] Each VA-ECHO program was run from a regional "hub" at 1 of 7 tertiary facilities. Primary care provider engagement in the program was voluntary.

All hubs followed similar procedures and reported to a centralized VA oversight body. Regional VA-ECHO videoconferences included brief didactics by specialists and collaborative discussions of cases electronically submitted by primary care providers. Videoconferences took place every 1 to 2 weeks and lasted 60 to 90 minutes. Each hub determined the curriculum for its region. Supplementary Table 1 (available online) shows a sample curriculum and the learning objectives from 1 regional program. Primary care providers implemented treatment plans within the primary care setting, with reconsultation if needed.

Human Subjects

This operational evaluation project was sponsored by the VA Office of Specialty Care Services/Specialty Care Transformation. The activities were undertaken in support of Veterans Health Administration operational programs and did not constitute research, in whole or in part, in compliance with Veterans Health Administration Handbook 1058.05. Therefore, institutional review board approval was not required.

Study Population

We identified all hepatitis C–infected patients in each primary care provider's panel using the Clinical Case Registry for Hepatitis C, a national registry including all hepatitis C–infected Veterans since 1999.[15] Hepatitis C viremia was confirmed by positive polymerase chain reaction, detectable viral genotype, or receipt of hepatitis C-specific medication. Patients were included if they were aged 18 to 80 years at baseline and if any primary care provider from their site participated in VA-ECHO during the study period. Patients were ineligible if receiving antiviral treatment at baseline ($n = 584$) or their viral genotype was other than 1 to 4 ($n = 15$). We excluded individuals whose latest viral load before the observation period was undetectable ($n = 2454$). We retrieved demographics, inpatient and outpatient International Classification of Diseases Clinical Modification 9th Revision codes, laboratory tests, and prescriptions using the Corporate Data Warehouse, a comprehensive repository of data from the VA's universal electronic medical record system.[16]

Assignment of Primary Care Provider

The primary care provider for exposed patients was defined by the majority of outpatient primary care visits after VA-ECHO consultation, plus at least 1 visit with the same provider before VA-ECHO referral. The primary care provider for unexposed patients was defined by the majority of outpatient primary care visits during the observation period, including a minimum of 3 visits.

Exposure Definition

Primary care provider exposure was defined by ≥1 electronic VA-ECHO referral request submitted between April 2011 and June 2015. To account for changes in exposure status, we considered patients unexposed before their primary care provider's first VA-ECHO consultation and exposed thereafter until the end of the evaluation. All hepatitis C–infected patients on a VA-ECHO primary care provider's panel were considered exposed, although primary care providers could select individual patients for review on a teleconference. Patients remained unexposed if their primary care provider never participated in VA-ECHO (Figure 1).

The start of follow-up time is termed the "baseline date" for each patient. Subjects began to accrue follow-up time at the later of the following: the first date subjects saw their primary care provider, the date of initial hepatitis C positivity, or January 1, 2010. Baseline rates of hepatitis C treatment initiation and sustained virologic response were evaluated for 16 months before VA-ECHO implementation for each primary care provider's panel.

Treating Provider Type and Specialty Referral

Type of provider (MD/DO, nurse practitioner, physician assistant, pharmacist) was defined by degree and clinical description. Specialty referral was identified by ≥1 outpatient visit with gastroenterology, hepatology, or infectious diseases within 30 days before or after treatment initiation.

Baseline Patient Characteristics

We identified predictors of treatment initiation and outcomes on the basis of previous literature. Demographics included age, sex, ethnicity (Hispanic/non-Hispanic), and race (white or nonwhite, based on self-report in VA records). Rural status was defined by US Census Bureau criteria applied to patients' ZIP code. Outpatient clinic types included community-based versus medical center-based clinics.

We extracted peripheral blood results for creatinine, aspartate aminotransferase, alanine aminotransferase, bilirubin, hemoglobin, international normalized ratio, viral genotype, and viral load from laboratory files using the most recent result before baseline. Anemia was defined as hemoglobin <12 g/dL (men) or <11 g/dL (women). We used standard formulas to calculate Fibrosis-4,[17] an index associated with advanced fibrosis and cirrhosis, and Model for End Stage Liver Disease score, a predictor of liver-related mortality.[18]

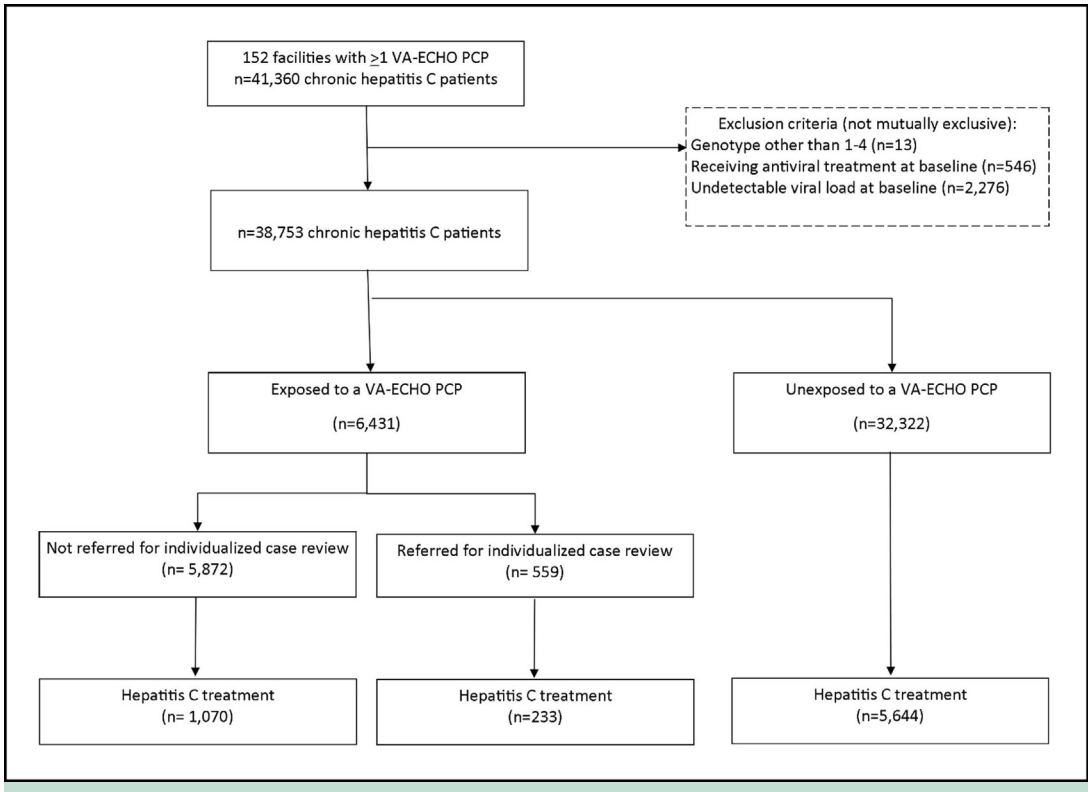

Figure 1 VA-ECHO exposure groups. PCP = primary care provider; VA-ECHO = Veterans Affairs Extension for Community Healthcare Outcomes.

Comorbidities were defined by ≥1 inpatient or ≥2 outpatient instances of International Classification of Diseases Clinical Modification 9th Revision codes previously validated in VA studies (Supplementary Table 2, available online). Comorbidities included cirrhosis, human immunodeficiency virus, diabetes, schizophrenia, bipolar disorder, depression, post-traumatic stress disorder, alcohol use disorder, and nonalcohol substance use disorder.[19-22] Overall medical disease burden was assessed using the Deyo modification of the Charlson comorbidity index.[23] We used pharmacy records to determine whether patients were treatment- experienced before baseline.

Antiviral Treatment Status and Outcome

We defined antiviral treatment as ≥1 prescription for a Food and Drug Administration–approved drug for hepatitis C virus. We calculated time to treatment as the time from baseline to first medication fill. Medication options available in the VA at the time of the study included ribavirin, interferon-α, pegylated interferon-α, boceprevir, telaprevir, sofosbuvir, simeprevir, sofosbuvir/ledipasvir, and ombitasvir/paritaprevir/ritonavir + dasabuvir. The VA maintains detailed, comprehensive antiviral treatment guidelines that are available to any VA clinician via the internet or from their facility's clinical pharmacy staff.[24]

Sustained virologic response was defined as undetectable hepatitis C polymerase chain reaction ≥12 weeks after the last antiviral prescription was exhausted (98% of viral relapses occur within 12 weeks of treatment cessation).[25] If any laboratory result showed positive viral load after completion of treatment, we determined that sustained virologic response was not obtained. If viral load was not assessed ≥12 weeks after treatment ended, then treatment outcome was missing. Patients with multiple treatments (n = 226) had multiple observations in the model.

Statistical Analysis

We used bivariate methods to compare characteristics of VA-ECHO–exposed and unexposed patients. Categoric variables were analyzed using chi-square tests, and continuous variables were analyzed using the Student *t* test.

We used Cox proportional hazards frailty modeling to assess the association between VA-ECHO exposure and time to antiviral treatment. Exposure to VA-ECHO was modeled as a patient-level time-varying covariate (nonexposed vs exposed) and adjusted for demographics, type of primary care site, rurality, prior antiviral treatment, Fibrosis-4 >3.25, Charlson-Deyo score, medical and psychiatric comorbidities, and baseline calendar year. Patients were censored for death or loss to follow-up (defined as 1 year without primary care provider follow-up). The frailty model accounted for clustering of results by primary care facility. The proportional hazards assumption was evaluated for each variable and found to be violated for calendar year. An interaction between calendar year and follow-up time was added to the model, and a likelihood ratio test confirmed improved fit.

To assess the relationship between VA-ECHO exposure and sustained virologic response, we examined all regimens completed through December 31, 2014, to allow sufficient time for 12 weeks of follow-up. Only 2 sofosbuvir/ledipasvir treatments were completed with ≥12 weeks follow-up time and were therefore excluded from analysis. We used a modified Poisson model generated from a generalized estimating equation to account for clustering by primary care facility.[26] Preliminary covariates included demographics, prior treatment, Fibrosis-4 >3.25, Charlson score, medical and psychiatric comorbidities, pretreatment viral load >800,000, type of antiviral regimen, and genotype. To avoid overfitting, we used backward selection to remove nonsignificant variables from the model (gender, substance abuse, diabetes, depression, site type, anemia, creatinine, post-traumatic stress disorder). By using similar procedures, we performed an exploratory analysis examining probability of treatment and virologic response among exposed patients with and without individual VA-ECHO case referrals.

RESULTS

Patient and Provider Characteristics

A total of 376 primary care providers (n = 152 sites) participated in VA-ECHO, encompassing 6431 unique hepatitis C–infected patients (**Figure 1**). Primary care providers submitted a median of 1 consult for review (interquartile range [IQR], 1-3; range, 1-74), for a total of 559 submissions (8.7% of hepatitis C-infected patients). A total of 3797 unexposed primary care providers associated with 32,322 patients were identified. Median patient follow-up time was 38.7 months (IQR, 23.8-57.2).

We found few meaningful differences in baseline characteristics across VA-ECHO exposure groups (**Table**). However, patients with an exposed primary care provider were more likely to be white (59% vs 53%) and less likely to be missing viral genotype (13% vs 17%). Exposed patients were more likely to be rural (25% vs 20%), less likely to receive primary care at a medical center (53% vs 70%), and less likely to receive primary care from a physician (65% vs 70%).

Antiviral Treatment Outcomes

A total of 6947 hepatitis C–infected patients initiated treatment (n = 7785 total regimens) (**Figure 2**). VA-ECHO exposure was associated with higher antiviral treatment initiation rates compared with nonexposure (adjusted hazard ratio, 1.20; 95% CI, 1.10-1.32; $P < .01$). Patients reviewed individually had higher incidence of treatment compared with unexposed patients (hazard ratio, 3.30; 95% CI, 2.78-3.90; $P < .01$). VA-ECHO patients without individualized case review had similar treatment rates compared with unexposed patients (hazard ratio, 1.03; 95% CI, 0.94-1.14; $P = .54$). Among treated patients, median time from exposure to treatment was 6.2 months (IQR, 2.5-17.0) for

Table Demographic and Clinical Characteristics by Veterans Affairs Extension for Community Healthcare Outcomes Exposure Group (N = 38,776)

	Exposed (n = 6431)	Unexposed (n = 32,322)	*P* Value
Age (mean, SD), y	57.9 (6.1)	57.7 (6.5)	.06
Male (%)	97.3	96.4	<.01
White (%)	58.7	52.7	<.01
Hispanic (%)	2.8	3.2	.08
Medical center (%)	53.4	70.2	<.01
Rural (%)	25.3	19.8	<.01
Medical diagnoses (%)			
Anemia	6.9	7.5	.09
Cirrhosis	6.4	6.1	.35
Diabetes	22.6	23.9	.03
HIV	1.8	2.3	.01
Creatinine >1.5 mg/dL	5.2	5.7	.12
Fibrosis-4 score >3.25	21.9	20.4	.01
Mental health and substance diagnoses (%)			
PTSD	23.0	21.1	<.01
Depression	37.4	36.6	.21
Schizophrenia	6.0	6.3	.48
Bipolar	7.7	7.6	.67
Alcohol use disorder	33.5	32.9	.40
Substance use disorder (excluding alcohol)	35.3	34.9	.63
Charlson Comorbidity Score, median (IQR)	1 (0-1)	1 (0-1)	.49
HCV characteristics			
Genotype			<.01
1	71.2	69.1	
2	8.9	7.8	
3	5.6	5.0	
4	0.8	0.7	
Missing	13.5	17.4	
Prior antiviral treatment	10.1	8.7	<.01

HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; PTSD = post-traumatic stress disorder; SD = standard deviation.

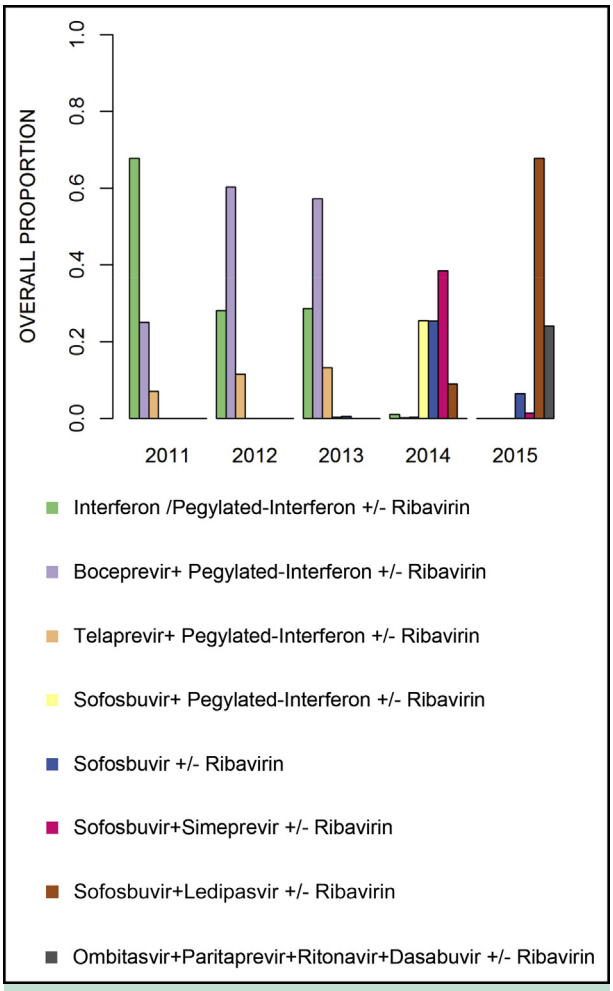

Figure 2 Hepatitis C treatment regimens among VA patients at VA-ECHO sites (2011-2015).

VA-ECHO–exposed patients who received individualized case review, 18.5 months (IQR, 7.4-28.3) for patients without case review, and 25.9 months (IQR, 11.9-50.2) from baseline to treatment in unexposed patients (Figure 3).

Among treated patients, specialty use was reduced in exposed patients with individualized case review (78.2%) compared with exposed patients without case review (87.9%) or unexposed patients (91.1%). Use of in-person specialty visits was lower in rural patients with individualized case review (73.6%) versus unexposed patients (91.4%). Among treated patients, primary care providers prescribed antiviral medications in 21.4% with individualized review, 3.4% without individualized case review, and 2.5% of unexposed patients (P <.01). We observed a consistent pattern of higher rates of primary care provider–initiated antiviral treatment in VA-ECHO–reviewed patients compared with unexposed patients across all regimen categories (interferon, protease inhibitor, all-oral direct-acting antiviral based) (data not shown).

Among treated patients with known treatment outcome (81% of regimens), the combined sustained virologic response rate across all regimens was 58.2% in VA-ECHO–exposed patients compared with 53.9% for unexposed patients. We observed no difference in the likelihood of sustained virologic response for VA-ECHO–exposed versus unexposed patients who received treatment, after adjustment for regimen and other predictors (adjusted rate ratio, 0.95; 95% CI, 0.86-1.05; P = .32). Sample size limitations precluded adjusted analysis of treatment response within subgroups, such as those with medication prescribed by primary care providers versus specialists. However, after stratifying by type of regimen, crude sustained virologic response rates were similar for primary care providers versus specialists. Finally, we examined the number of weeks on treatment by VA-ECHO exposure status for each type of regimen and found nearly identical durations, suggesting that VA-ECHO exposure is not associated with early discontinuation (data not shown).

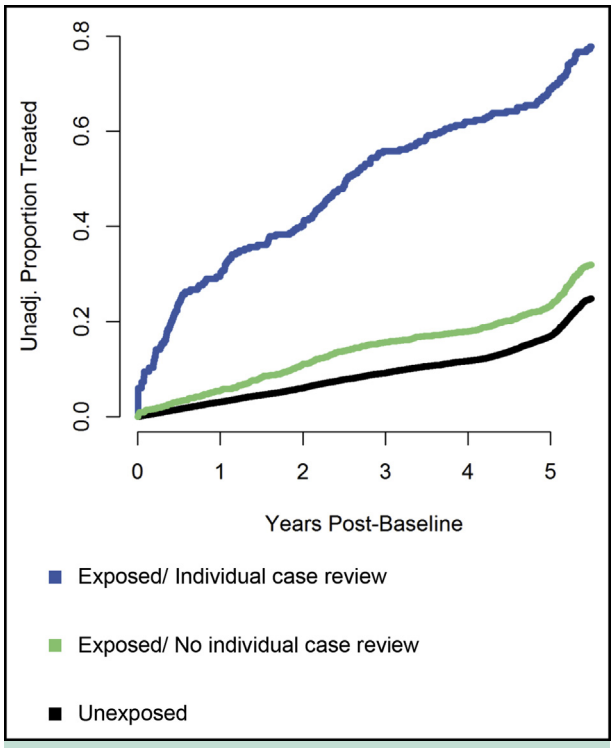

Figure 3 Time to hepatitis C virus treatment by VA-ECHO exposure.

DISCUSSION

This study evaluated the effect of a primary care–oriented telemedicine program on rates of hepatitis C treatment initiation and sustained virologic response in the national VA healthcare system. Hepatitis C–infected patients whose primary care providers requested individualized specialty case review through VA-ECHO were more likely than unexposed patients to receive antiviral treatment, with equivalent cure rates. In-person specialty visits were used less often among patients receiving VA-ECHO case review compared with unexposed patients (78.2% vs 91.1%), especially in rural areas (73.6% vs 91.4%). Our findings illustrate that primary care provider access to hepatitis C specialist support may enhance treatment rates without increasing the burden on in-person specialty services. Our analysis expands prior work by establishing the effectiveness of the ECHO approach in promoting primary care–based hepatitis C virus treatment across a national integrated health setting.[12]

Multiple aspects of VA-ECHO likely contributed to the association with antiviral treatment initiation. First, patients may be more likely to pursue treatment when it is convenient and accessible. Second, qualitative analysis suggests that hepatitis C–infected patients perceive fewer communication barriers with primary care providers compared with specialists.[27] We considered the possibility that primary care providers involved in VA-ECHO might simply refer more of their patients to specialty services. Although specialists continued to prescribe the majority of treatments, patients with VA-ECHO case review were more likely to receive antiviral medication from a primary care provider. Our results support the hypothesis that the option of receiving antiviral therapy from a primary care provider may remove an important treatment barrier for some individuals.

Even in the era of direct-acting antivirals, treatment by primary care providers primarily occurred in the context of individualized specialist case review, with few treatments initiated by primary care providers on their own. One possible explanation is that primary care providers feel unprepared to treat patients independently. Some facilities may require specialist review before authorizing primary care providers to order hepatitis C medication. Last, primary care providers may need to participate longer in VA-ECHO before becoming independent. Our findings imply that ongoing specialist support is important to realizing the benefits of VA-ECHO, at least with respect to antiviral treatment initiation. Future study is required to determine the level of specialist support needed by primary care providers as antiviral regimens become increasingly simple.

The cost-effectiveness and sustainability of programs like VA-ECHO remain to be demonstrated. For capitated health care delivery systems, such as Accountable Care Organizations, leveraging specialist time efficiently may help control the steep costs of hepatitis C treatment. Primary care provider–driven hepatitis C care could reduce the burden on subspecialty services, especially in underserved areas. However, networks that implement ECHO must be prepared to support the necessary specialist time. In addition, besides the universal obstacle of limited primary care provider time, significant barriers exist for primary care providers in the private sector to prescribe hepatitis medication (eg, insurance company preauthorization for hepatitis C drugs).

Further exploration is needed to discover whether some types of facilities or providers benefit differently from access to telemedicine support. Primary care providers participating in telementorship may gain professional satisfaction and confidence, as well as clinical knowledge.[5,28] Primary care providers appreciate the supportive networks they develop with colleagues through the ECHO model.[5] However, although greater exposure to VA-ECHO might conceivably produce more benefits, the optimal "dose" of telemedicine support is unclear to sustain competency in treating hepatitis C.

Study Limitations

Our findings are tempered by several strengths and limitations. We benefitted from near-complete ascertainment of laboratory and pharmacy data through the VA's comprehensive electronic medical record across a large and geographically diverse population. In terms of limitations, each VA region had the authority to tailor its didactic curriculum to the needs of its learners. Therefore, curricula were somewhat heterogeneous, although all were structured similarly and overseen centrally. Second, although we adjusted for several important provider characteristics (eg, primary care provider

professional background) and compared patients with controls from their own facilities, participation in VA-ECHO was voluntary and therefore involved self-selected providers motivated to treat hepatitis C. Future randomized trials of the ECHO model would help to clarify its effect.

CONCLUSIONS

For the VA, disseminating hepatitis C treatment is a crucial organizational priority given increasing disease sequelae such as cirrhosis and liver cancer.[3] As an integrated system, the VA was able to systematically implement VA-ECHO and invest in primary care provider participation on a national scale. Our results provide reassurance that specialized telemedicine support for primary care providers can expand access to hepatitis C virus treatment, without decrements in sustained virologic response or increases in face-to-face specialty visits.

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Conflict of Interest: The sponsor authorized the concept for the project but had no direct role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication. SRK is employed by the VA Office of Specialty Care Transformation. DR is employed by the Veterans Affairs Office of HIV, Hepatitis C, and Public Health Pathogens.

Authorship: All authors had access to the data and played a role in writing this manuscript.

SUPPLEMENTARY DATA

Supplementary tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2016.11.019.

APPENDIX

Supplementary Table 1 Sample Curriculum and Learning Objectives for a Veterans Affairs Extension for Community Healthcare Outcomes Regional Program

Title	Learning Objectives ("By the end of this talk, learners should be able to …")
HCV Treatment Update	List the indications, advantages, and limitations of emerging treatments for HCV
Renal Complications of HCV	List the major renal complications of HCV; describe the pathophysiology and treatment of HCV-related renal disease
HCV Treatment in Special Populations	Describe management of patients with HCV and (1) decompensated cirrhosis, (2) end-stage renal disease, or (3) genotype 3 HCV
Alcoholic Hepatitis	Describe the clinical presentation of acute alcoholic hepatitis; determine the indication for prednisolone therapy using Maddrey's discriminant function; appreciate the evolving therapeutic options for acute alcoholic hepatitis
Pretransplant Psychosocial Evaluation	Describe the goals of preliver transplant evaluation; identify common psychosocial obstacles to successful transplant listing
Extrahepatic Manifestations of HCV	Describe the relationship between HCV and renal diseases including MPGN cryoglobulinemic vasculitis and membranous nephropathy; describe available treatments for HCV-related renal disease
Hyponatremia in Cirrhosis	Define hyponatremia in both the general population and the cirrhosis population; describe the pathophysiology of hyponatremia in cirrhosis; list management strategies for hyponatremia in cirrhosis
Diagnosis and Management of Varices	Describe the prognostic implications of varices vs variceal hemorrhage; describe evidence-based management strategies for varices and variceal hemorrhage prophylaxis
Lung-Liver Syndromes	Describe the pulmonary consequences of liver disease; describe the relationship between the liver and pulmonary vasculature; understand how to diagnose and manage portopulmonary hypertension
Perioperative Care in Patients with Cirrhosis	List the benefits and limitations of major clinical tools used in estimating perioperative mortality in patients with cirrhosis
Primary Care Issues in the Long-Term Management of Patients Postliver Transplant	Describe the indications for liver transplant; list the expectations for the primary care of patients postliver transplant
Resistance-Associated Variant Testing	Describe resistance-associated variants and their impact on HCV treatment outcomes; list the 3 classes of resistance-associated variants; describe strategies for dealing with resistance-associated variants
Cannabis and Liver Disease	Describe the effects of cannabis use on progression of HCV and other liver diseases; describe the impact of cannabis use on treatment for HCV
Spontaneous Bacterial Peritonitis	Discuss the diagnosis and management of spontaneous bacterial peritonitis
HCV in Women	Describe the natural history of HCV in women; list gender-specific concerns for women with HCV (eg, pregnancy and breastfeeding, vertical transmission); describe HCV outcomes in women
HIV-HCV coinfection	Report the major epidemiologic features of HCV in patients coinfected with HIV; describe the indications, benefits, and therapeutic considerations related to HCV treatment in persons with HIV
Pain Management in Patients with Cirrhosis	Describe differences in drug metabolism in patients with chronic liver disease; list the benefits and limitations of major analgesic classes in patients with chronic liver disease
Hepatic Encephalopathy	Describe the pathophysiology of hepatic encephalopathy; describe the relative utility of physical examination findings, scoring algorithms, and ammonia levels in the diagnosis of encephalopathy; implement a management strategy to prevent or treat hepatic encephalopathy
Ascites	Discuss the pathophysiology and management of ascites in patients with liver disease
Understanding Hepatitis B Virus Testing	List indications for HBV screening; interpret basic hepatitis B serologies, including sAb, sAg, and eAg; identify indications for antiviral treatment in chronic HBV
Drug interactions with DAAs	Understand the mechanism of drug interactions; know the tools available to identify interactions; review common drug interactions; describe management options of drug interactions.

Supplementary Table 1 Continued

Title	Learning Objectives ("By the end of this talk, learners should be able to …")
Assessing the Risk of Substance Relapse in Liver Transplant Recipients	List the major considerations for assessing substance relapse in patients post-transplant; describe strategies for relapse prevention in patients post-transplant
Use of Nonselective Beta-Blockers in Cirrhosis	Review the pharmacology of nonselective beta-blockers and their role in patients with cirrhosis; explore the ongoing controversy involving nonselective beta-blockers in patients with spontaneous bacterial peritonitis or ascites
Autoimmune Liver Disease	Report the pathophysiologic mechanisms of autoimmune hepatitis, PSC, and PBC; describe the diagnostic criteria for autoimmune liver diseases; describe treatment options for autoimmune liver diseases
Abnormal Liver Function Test Results	Interpret liver blood test results; implement a systematic approach to abnormal liver blood test results; describe indications for liver biopsy
Evidence-based Liver Examination	Identify evidence-based physical examination findings in cirrhosis; describe the specific examination findings linked to portal hypertension, synthetic failure, and increased peripheral estrogen
Medical Management of the Preliver Transplant Recipient	Describe the process of transporting a patient to transplant, including timing for referral, common barriers to transplant, and navigating the peritransplant period
Nutrition and Alcoholism	Understand the relationship between alcohol and malnutrition; identify nutritional deficiencies that are common in alcoholism
Understanding Imaging Modalities for the Liver	Describe the indications, benefits, and limitations of various liver imaging modalities (ultrasound, computed tomography, and magnetic resonance imaging)
Hepatocellular Carcinoma	Describe risk factors for HCC; describe the rationale and limitations of HCC surveillance
Hepatitis B Treatment	Report how to use HBV test results, laboratory tests, and other data to determine treatment candidacy; describe HBV treatment goals; list pharmacologic options for treating HBV
Hepatic Vascular Disorders	Describe the clinical significance of chronic portal vein thrombosis, acute portal vein thrombosis, and hepatic vein thrombosis; determine when hepatic vascular thrombosis requires anticoagulation
Hepatorenal Syndrome	Describe the pathophysiology of neurohormonal dysregulation that causes ascites and hepatorenal syndrome; describe how to diagnose and treat hepatorenal syndrome
CAM in Patients with Liver Disease	Describe the evidence for and against silymarin in patients with HCV; describe the prevalence of CAM in patients with liver disease; identify resources to assess the safety of CAM products for the liver

CAM = complementary and alternative medicine; DAA = direct-acting antiviral; eAg = envelope antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MPGN = membranoproliferative glomerulonephritis; PBC = primary biliary cholangitis; PSC = primary sclerosing cholangitis; sAb = surface antibody; sAg = surface antigen.

Supplementary Table 2 International Classification of Diseases Clinical Modification 9th Revision Codes Used in Comorbidity Definitions

	ICD-9 Codes
Alcohol	305.0-305.03, 303.9-303.93, 291.81, 291.0, 291.8, 291.9, 303.00, 577, 357, 425.5, 980.9, 571.0X, 571.1X, 571.3X, 571.2
Bipolar	296.00-296.06, 296.50-296.54, 296.56, 296.60, 296.66, 296.7, 296.80
Cirrhosis	456.0, 456.1, 456.2, 456.20, 456.21, 567.2, 567.23, 571.2, 571.5, 572.2, 572.4
Diabetes	250.00-250.93, 648.00-648.09, V18.0, V177.1, 357.2, 362.0, 366.41, 536.3
Depression	296.20-296.26, 296.30-296.36, 296.90, 300.4, 311
HIV	042-044.9
PTSD	309.81
Schizophrenia	295.0-295.9
Substance abuse	305.2-305.9, 304.0-304.9, 292.0

HIV = human immunodeficiency virus; ICD-9 = International Classification of Diseases Clinical Modification 9th Revision; PTSD = post-traumatic stress disorder.