

ORIGINAL ARTICLE

Outcomes of Treatment for Hepatitis C Virus Infection by Primary Care Providers

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ABSTRACT

BACKGROUND

The Extension for Community Healthcare Outcomes (ECHO) model was developed to improve access to care for underserved populations with complex health problems such as hepatitis C virus (HCV) infection. With the use of video-conferencing technology, the ECHO program trains primary care providers to treat complex diseases.

METHODS

We conducted a prospective cohort study comparing treatment for HCV infection at the University of New Mexico (UNM) HCV clinic with treatment by primary care clinicians at 21 ECHO sites in rural areas and prisons in New Mexico. A total of 407 patients with chronic HCV infection who had received no previous treatment for the infection were enrolled. The primary end point was a sustained virologic response.

RESULTS

A total of 57.5% of the patients treated at the UNM HCV clinic (84 of 146 patients) and 58.2% of those treated at ECHO sites (152 of 261 patients) had a sustained viral response (difference in rates between sites, 0.7 percentage points; 95% confidence interval, -9.2 to 10.7; $P=0.89$). Among patients with HCV genotype 1 infection, the rate of sustained viral response was 45.8% (38 of 83 patients) at the UNM HCV clinic and 49.7% (73 of 147 patients) at ECHO sites ($P=0.57$). Serious adverse events occurred in 13.7% of the patients at the UNM HCV clinic and in 6.9% of the patients at ECHO sites.

CONCLUSIONS

The results of this study show that the ECHO model is an effective way to treat HCV infection in underserved communities. Implementation of this model would allow other states and nations to treat a greater number of patients infected with HCV than they are currently able to treat. (Funded by the Agency for Healthcare Research and Quality and others.)

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This article (10.1056/NEJMoa1009370) was published on June 1, 2011, at NEJM.org.

N Engl J Med 2011;364:2199-207.
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THE EXTENSION FOR COMMUNITY HEALTH-care Outcomes (ECHO) model was developed by the University of New Mexico (UNM) Health Sciences Center as a platform for both delivery of services and outcomes research.^{1,2} The objectives of the ECHO program are to improve the access of minorities and other underserved populations to best-practice care for hepatitis C virus (HCV) infection, to determine the safety and efficacy of treatment for HCV infection based on the ECHO model in rural communities, and to compare the effectiveness of the ECHO model with that of university-based clinic treatment. The ECHO program increases the accessibility of populations outside urban areas to the specialized medical resources of academic medical centers.

An estimated 170 million patients worldwide have chronic HCV infection; 3.2 million of these patients live in the United States.^{3,4} Many patients were infected in the 1970s and 1980s, leading to a rising tide of cirrhosis and hepatocellular carcinoma.⁵ Chronic HCV infection accounts for 10,000 deaths each year in the United States and is the leading reason for liver transplantation.^{6,7}

Fortunately, treatment for HCV is available and cost-effective; it cures 45% of patients with HCV genotype 1 infection and 75% of patients with HCV genotype 2 or genotype 3 infection.⁸⁻¹¹ A sustained virologic response permanently halts the progression of liver disease, reverses fibrosis in many patients, and reduces the risk of hepatocellular carcinoma. However, the treatment is complex. Pegylated interferon (peginterferon) and ribavirin are associated with serious side effects that require aggressive management by multidisciplinary experts.⁹⁻¹¹

Despite advances in treatment and remarkable improvements in cure rates, very few persons with chronic HCV infection are receiving treatment. The total number of prescriptions for HCV antiviral medications declined by 34% between 2002 and 2007. If this trend continues, it is estimated that treatment will prevent only 14.5% of potential liver-related deaths caused by HCV infection between 2002 and 2030.¹² Members of racial and ethnic minorities and older patients are less likely than other patients to receive needed care.¹³⁻¹⁶

The reasons for the inadequacy of and insufficient access to treatment for HCV infection are complex and not completely understood. Historically, few primary care clinicians have offered treat-

ment for HCV infection in rural areas and prisons, owing to a lack of training.¹⁷ In 2004, patients from rural areas had to wait up to 6 months for an appointment at the UNM HCV clinic and had to travel up to 250 miles. A typical patient with HCV genotype 1 infection would have to make an average of 18 trips during the course of treatment. Major barriers to care also exist among prison inmates. According to data from the Department of Corrections, 40% of the 6000 inmates in the New Mexico Department of Corrections are infected with HCV. As of 2003, not a single patient in the correctional system had received treatment for HCV infection.

Lack of access to specialty care services at community-based health centers is a major problem, particularly for uninsured patients.^{18,19} Community-based health centers are often the most culturally appropriate and accessible choices for care, particularly in rural areas, and providers at these centers can establish trust through ongoing relationships with patients. Therefore, these centers can be ideal places to provide complex care for HCV infection — if they have access to the needed expertise.

METHODS

ECHO MODEL

With the use of state-of-the-art telehealth technology, the ECHO program offers primary care providers from underserved areas training, advice, and support in delivering best-practice care for patients with complex health conditions such as chronic HCV infection. At each of the ECHO partner sites, providers participating in the program include a lead clinician (a physician, nurse practitioner, or physician's assistant) and a nurse or medical assistant, who helps manage patient care. Before joining the ECHO network, none of the community practice sites had treated patients with HCV infection.

Community providers take part in weekly HCV clinics, called "knowledge networks," by joining a video conference or calling into a teleconference line (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The providers present their cases by sharing patients' medical histories, laboratory results, treatment plans, and individual challenges and ask questions about best practices. Specialists at the UNM Health

Sciences Center from the fields of hepatology, infectious diseases, psychiatry, and pharmacology provide advice and clinical mentoring during these clinics. Working together, the community providers and specialists manage the patients' care according to evidence-based protocols. These case-based discussions are supplemented with short didactic presentations by interdisciplinary experts to improve content knowledge.

This case-based approach creates a "learning loop," in which extensive knowledge is imparted, skills are taught, and self-efficacy is encouraged in several ways. Longitudinal comanagement of illnesses with specialists allows community providers to practice their expanded knowledge and skills in a manner that builds self-efficacy in handling real-world situations with their patients, while ensuring that they follow best practices as they learn. Learning from other community-based providers who have faced similar challenges and clinical situations is facilitated through shared case-management decision making.

Currently, there are 16 community sites and 5 prisons in which treatment for HCV infection is delivered with the use of the ECHO model. Since ECHO's inception in 2003, there have been more than 5000 case presentations, and 800 patients have been treated. We conducted a prospective cohort study to assess the safety and efficacy of treatment based on the ECHO model, as compared with treatment at a university HCV clinic. Our hypothesis was that when treatment for HCV infection is delivered in the community (or prison) with the use of the ECHO model, it is as effective as that provided at the academic medical center.

STUDY POPULATION

Patients could be included in the ECHO or UNM (active-control) cohort if they were between 18 and 65 years of age, had evidence of chronic HCV infection with detectable HCV RNA, had not received treatment for HCV infection before September 7, 2004, and initiated treatment between September 7, 2004, and February 29, 2008 (for patients with HCV genotype 1 or 4 infection) or between September 7, 2004, and August 15, 2008 (for patients with HCV genotype 2 or 3 infection). Since HCV genotype 1 and genotype 4 infections require a longer duration of treatment, this distinct timing allowed us to identify a definitive

outcome for all subjects within the cohort before December 31, 2009.

Patients were excluded if they had an absolute neutrophil count of less than 1500 per cubic millimeter, a platelet count of less than 75,000 per cubic millimeter, a creatinine level higher than 2.0 mg per deciliter (176.8 μ mol per liter), coinfection with human immunodeficiency virus or hepatitis B virus, a history of a solid-organ transplantation, or decompensated liver disease.

STUDY DESIGN

This study had a prospective cohort design. All patients received standard treatment for HCV infection (according to the ECHO clinical protocol), with peginterferon administered at standard doses and ribavirin administered at doses based on the patient's weight (for patients with all genotypes). Early in the study period, the duration of treatment was based on genotype alone (48 weeks for patients with genotype 1 or genotype 4 infection and 24 weeks for patients with other genotypes). Starting in September 2006, the treatment period was extended for patients who had a slow response to therapy. Growth factors were administered as clinically indicated. Clinical adverse events were monitored throughout the study. The aspartate aminotransferase:platelet ratio index (APRI) was used to estimate the extent of fibrosis and cirrhosis. The higher the APRI score, the more likely a patient is to have extensive fibrosis or cirrhosis.

The study was approved by the institutional review board at the UNM Health Sciences Center. The requirement for informed consent was waived because all patients received care according to accepted standards and the data that were collected were considered to be part of routine care.

END POINT

The primary end point was a sustained virologic response, which was defined as an undetectable HCV RNA level 24 weeks after the end of treatment. All patients who received at least one dose of interferon were included in the analysis. Subjects without follow-up data were considered to have had treatment failure.

ASSESSMENT OF SAFETY

Safety was assessed by means of laboratory testing and through information obtained at visits

on weeks 1, 2, and 4 and monthly thereafter. Serious adverse events were reported and investigated. An independent data and safety monitoring committee evaluated all serious adverse events.

STATISTICAL ANALYSIS

Continuous variables are expressed as means \pm SD. Differences between the groups in continuous variables were analyzed with the use of Student's *t*-test (with 95% confidence intervals) or the Mann-Whitney *U* test. *P* values of less than 0.05 were considered to indicate statistical significance. Since this study was not randomized, multivariate analysis was used to verify that the two treatments did not differ significantly after adjustment for demographic and baseline clinical characteristics of the patients. Stepwise logistic regression was used to identify predictors of sustained virologic response that might be confounders, including age; sex; race or ethnic group; marital status; employment status; housing status; route of transmission; height, weight, and body-mass index (BMI); HCV viral load; genotype; APRI score; levels of blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, total protein, albumin, and hemoglobin; white-cell, platelet, and absolute neutrophil counts; red-cell distribution width; and mean corpuscular volume.

RESULTS

PATIENTS

During the study period, 519 patients were started on treatment for HCV infection. A total of 112 patients were excluded, leaving 407 who were included in the analysis (Fig. 1). There were baseline differences between the two cohorts (Table 1). The ECHO cohort, as compared with the UNM cohort, included a significantly higher proportion of men (96% of the patients treated in the prison system were men) and a larger percentage of Hispanics, and the patients in the ECHO cohort had higher values for mean weight and BMI. In addition, the patients at the UNM HCV clinic were older than the patients in the ECHO cohort. Approximately 56% of the patients in each group had HCV genotype 1 infection.

VIROLOGIC RESPONSE

A total of 58.2% of the patients at the ECHO sites (152 of 261 patients) had a sustained virologic

response, a rate that did not differ significantly from that among patients at the UNM HCV clinic (57.5%, 84 of 146 patients). The between-group difference was 0.7 percentage points (95% confidence interval [CI], -9.2 to 10.7). The overall rate of sustained virologic response among patients with HCV genotype 1 infection was 48.3%. (See Table 2 for the rates of sustained virologic response according to genotype and site.) Stepwise multivariable logistic-regression analyses identified several clinical factors as independent predictors of sustained virologic response: genotype 1, alanine aminotransferase level, and APRI score (Table 3). After adjustment for patient characteristics, the rate of sustained virologic response did not differ significantly according to the site of treatment (UNM clinic or ECHO site) (adjusted odds ratio at ECHO site vs. UNM, 1.04; 95% CI, 0.67 to 1.60).

SAFETY

Overall, more patients in the UNM HCV clinic cohort than in the ECHO cohort had a serious adverse event (13.7% vs. 6.9%, $P=0.02$). In addition, more patients in the UNM HCV clinic cohort than in the ECHO cohort had a serious adverse event leading to termination of treatment (8.9% vs. 4.2%, $P=0.05$) (Table 4).

DISCUSSION

In this community-based study, we found that treatment for HCV infection delivered with the use of the ECHO model was associated with high rates of cure. The rates of sustained virologic response in our ECHO cohorts (58.2% overall and 49.7% among patients with HCV genotype 1 infection) were similar to those among patients in the study's comparison group, who were treated at an academic medical center, and to the rates reported in licensing trials of peginterferon and ribavirin for the treatment of HCV infection.⁹⁻¹¹ Previous community-based treatment studies have failed to replicate the results of licensing trials. For example, in the Weight-Based Dosing of Peginterferon alfa-2b and Ribavirin trial (WIN-R; ClinicalTrials.gov number, NCT00299936),²⁰ the rate of sustained viral response was 34% among patients with HCV genotype 1 infection. The Veterans Affairs observational cohort study conducted at 121 facilities showed a rate of sustained viral response of 20% among patients with HCV genotype 1 infection.²¹

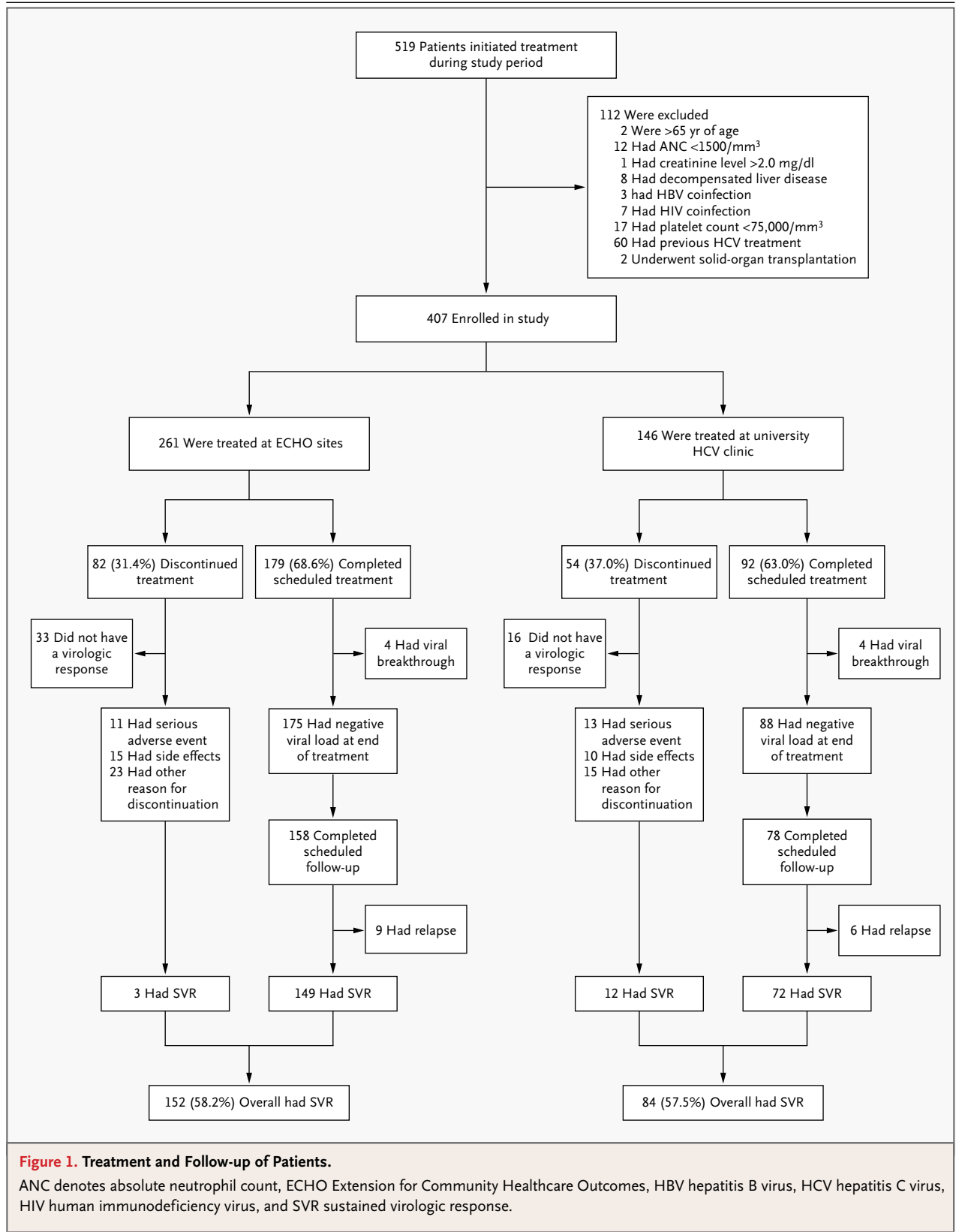


Figure 1. Treatment and Follow-up of Patients.

ANC denotes absolute neutrophil count, ECHO Extension for Community Healthcare Outcomes, HBV hepatitis B virus, HCV hepatitis C virus, HIV human immunodeficiency virus, and SVR sustained virologic response.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	ECHO Sites (N=261)	UNM HCV Clinic (N=146)	P Value
Age — yr	41.9±9.8	45.4±9.8	0.001
Male sex — no. (%)	190 (72.8)	66 (45.2)	<0.001
Race or ethnic group — no. (%)†			
White	244/256 (95.3)	134/146 (91.8)	0.15
American Indian	8/256 (3.1)	3/146 (2.1)	0.53
Black	4/256 (1.6)	3/146 (2.1)	0.72
Asian or Pacific Islander	0	6/146 (4.1)	0.001
Hispanic — no./total no. (%)‡	156/242 (64.5)	60/145 (41.4)	<0.001
Weight — kg	85.3±15.9	80.3±17.7	0.007
Body-mass index§			
Mean	29.4±5.3	28.1±5.7	0.03
≤24.9 — no./total no. (%)	47/246 (19.1)	45/144 (31.2)	0.006
25.0–29.9 — no./total no. (%)	97/246 (39.4)	54/144 (37.5)	0.71
≥30.0 — no./total no. (%)	102/246 (41.5)	45/144 (31.2)	0.05
ALT — U/liter	103±78	97±73	0.44
APRI score¶	0.935±0.910	0.938±0.847	0.97
Log ₁₀ viral load	5.92±0.94	5.84±1.01	0.43
HCV genotype 1 — no. (%)	147 (56.3)	83 (56.8)	0.50

* Plus–minus values are means ±SD. ALT denotes alanine aminotransferase, ECHO Extension for Community Healthcare Outcomes, HCV hepatitis C virus, and UNM University of New Mexico.

† Race or ethnic group was determined by the provider.

‡ Data on Hispanic versus non-Hispanic ethnic group were missing for 20 patients.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ The aspartate aminotransferase (AST):platelet ratio index (APRI), which was used to estimate the extent of fibrosis and cirrhosis, is calculated according to the following formula: [(AST level ÷ upper limit of the normal range) ÷ platelet count (10⁹ per liter)] × 100. The higher the APRI score, the more likely a patient is to have extensive fibrosis.

Our study cohort, particularly at the ECHO sites, was predominately Hispanic. We met our goal of increasing treatment for minority and other underserved patients. A recent study by the Latino Study Group (NCT00107653) showed that for patients with HCV genotype 1 infection, the rates of sustained virologic response were significantly lower among Hispanic patients than among non-Hispanic patients (34% vs. 49%).²² We did not see a difference in sustained virologic response between Hispanic and non-Hispanic patients in our study. Research suggests that disparities in treatment according to race or ethnic group may be due to geographic differences resulting in inadequate access to high-quality care, particularly specialty care.^{23–25} Treatment with the use of the ECHO model overcomes this barrier by bringing to the rural clinician the expertise and clinical

resources that may not otherwise be available, thus positively affecting the outcomes.

Our study design has three principal limitations. First, there was no comparison group comprising patients who were treated in rural settings without the ECHO model. The barriers to treatment are so formidable and concerns for safety so great that in 2004 almost no patients with HCV infection in rural and frontier areas of New Mexico were receiving treatment. Second, we were unable to randomly assign providers to a group using the ECHO model or a control group without ECHO support because we could not ethically encourage control providers to treat HCV infection without training; in addition, we could not randomly assign patients owing to the nature of the study. Third, in a prospective cohort study, multivariate models can adjust for differences in patient

Table 2. Sustained Virologic Response According to Genotype and Site of Treatment.*

HCV Genotype	ECHO Sites <i>no. of patients with response/total no. (%)</i>	UNM HCV Clinic	Difference between ECHO Sites and UNM HCV Clinic	P Value
			<i>percentage points (95% CI)</i>	
All genotypes	152/261 (58.2)	84/146 (57.5)	0.7 (−9.2 to 10.7)	0.89
Genotype 1	73/147 (49.7)	38/83 (45.8)	3.9 (−9.5 to 17.0)	0.57
Genotype 2 or 3	78/112 (69.6)	42/59 (71.2)	−1.5 (−15.2 to 13.3)	0.83

* The rates of sustained virologic response are not reported separately for six patients with genotype 4 or genotype 6. ECHO denotes Extension for Community Healthcare Outcomes, HCV hepatitis C virus, and UNM University of New Mexico.

Table 3. Odds Ratio for Sustained Virologic Response in Univariate and Multivariate Models.*

Variable	Univariate Model		Best Multivariate Model†	
	Odds Ratio for Virologic Response (95% CI)	P Value	Adjusted Odds Ratio for Virologic Response (95% CI)	P Value
ECHO sites vs. UNM HCV clinic	1.03 (0.68–1.55)	0.89	1.10 (0.71–1.70)	0.68
ALT, per 10-unit-per-liter increase			1.05 (1.01–1.09)	0.01
White-cell count, per 1000-cell-per-microliter decrease			0.86 (0.76–0.97)	0.02
APRI score, per 1-unit increase			0.43 (0.30–0.62)	<0.001
Genotype 1, vs. genotype 2 or 3			0.40 (0.26–0.62)	<0.001

* ALT denotes alanine aminotransferase, and APRI aspartate aminotransferase (AST):platelet ratio index.

† P=0.44 by the Hosmer–Lemeshow test for goodness of fit. The best multivariate model was determined by stepwise logistic regression of sustained viral response. The comparison of the univariate model with the multivariate model shows that the similarity of the results of treatment at Extension for Community Healthcare Outcomes (ECHO) sites as compared with the University of New Mexico (UNM) hepatitis C virus (HCV) clinic with respect to sustained virologic response was not significantly modified by the “best” covariates, even though these covariates were important predictors of sustained virologic response. Other candidate variables included age; sex; race or ethnic group; marital status; employment status; housing status; route of transmission; height, weight, and body-mass index; hepatitis C viral load; levels of blood urea nitrogen, creatinine, AST, alkaline phosphatase, total bilirubin, total protein, albumin, and hemoglobin; red-cell distribution width; mean corpuscular volume; absolute neutrophil count; and platelet count.

characteristics that are measured but do not address those that are not or cannot be measured.

Although the rate of sustained virologic response did not differ significantly according to the site of treatment (ECHO site vs. UNM HCV clinic) in the multivariate model, the confidence interval for the odds ratio was quite broad. This result is consistent with a substantial difference in the outcome of care between the ECHO sites and the UNM HCV clinic. The study was not large enough to establish equivalence.

The results of this study show that the ECHO model is an effective way to treat HCV infection in rural and underserved communities. By implementing this model, other states and nations

can potentially treat many more patients infected with HCV than are currently receiving treatment, thereby reducing the enormous burden of illness and associated mortality. There are a number of potential explanations for the success of the ECHO model. Community providers, particularly community-based health centers, provide coordinated, patient-centered care in facilities proximate to their patients. Patients are likely to have greater trust in local providers, who tend to be culturally competent with respect to their specific communities. This may enhance patients' adherence to treatment and allow for greater direct contact with the clinician, including more frequent visits. As a result, local providers may be

Table 4. Serious Adverse Events According to Site of Treatment.*

Serious Adverse Event	ECHO Site (N=261)	UNM HCV Clinic (N=146)	P Value
	number (percent)		
Any	18 (6.9)	20 (13.7)	0.02
Hematologic disorders	0	2 (1.4)	
Cardiovascular disorders	0	3 (2.1)	
Gastrointestinal and hepatobiliary disorders	7 (2.7)	4 (2.7)	
Infections	3 (1.1)	5 (3.4)	
Psychiatric disorders	3 (1.1)	2 (1.4)	
Other disorders	5 (1.9)	4 (2.7)	
Treatment-related	13 (5.0)	15 (10.3)	
Leading to discontinuation of treatment	11 (4.2)	13 (8.9)	0.05

* ECHO denotes Extension for Community Healthcare Outcomes, HCV hepatitis C virus, and UNM University of New Mexico.

better able to comply with best-practice protocols, ensure close assessment of the results of laboratory tests, offer education tailored to the patient, and provide better and more timely management of side effects. In addition, the fact that the primary care of the patient and the management of hepatitis are provided by the same clinician ensures better coordination of care and fewer communication challenges.

As a result of the success of the model for treatment of HCV infection, the ECHO program has been expanded to 255 sites. These clinics address common and complex health issues, including substance-use disorders, cardiac risk factors, chronic pain, asthma, rheumatologic conditions, and other disorders. The project shows that technological tools and interdisciplinary collaboration can be used to leverage scarce resources for specialty care.

In conclusion, we found that HCV infection, which is a complex disease, can be managed as

effectively at a center that uses the ECHO model as at an academic medical center. ECHO represents a needed change from the conventional approaches in which specialized care and expertise are available only at academic medical centers in urban areas. The ECHO model has the potential for being replicated elsewhere in the United States and abroad, with community providers and academic specialists collaborating to respond to an increasingly diverse range of chronic health issues.

Supported by the Agency for Healthcare Research and Quality (Health Information Technology Grant UC1 HS015135 and Minority Research Infrastructure Support Program grant R24HS16510), the Robert Wood Johnson Foundation, the New Mexico Department of Health, and the New Mexico State Legislature.

Dr. Arora reports receiving grant support from ZymoGenetics, Genentech, Vertex Pharmaceuticals, Tibotec, Human Genome Sciences, and Wyeth (now part of Pfizer), speaking fees from Schering-Plough (now part of Merck) and Genentech–Roche, and payment for advisory-board membership from Vertex Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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