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Prevalence and Treatment of Chronic Hepatitis C Virus Infection in the US Department of Veterans Affairs

Lauren A. Beste* and George N. Ioannou

* Correspondence to Dr. Lauren A. Beste, Veterans Affairs Puget Sound Health Care System, 1660 South Columbian Way, S-111-GI, Seattle, WA 98108 (e-mail: lauren.beste@va.gov).

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Chronic hepatitis C virus (HCV) is the most common blood-borne pathogen in the United States. HCV disproportionately affects Veterans Affairs (VA) health-care users: 174,302 HCV-infected veterans were in VA care in 2013, making the VA the world's largest HCV care provider. This systematic review identified 546 articles related to HCV in the VA. After assessment by 2 independent reviewers, 28 articles describing prevalence and treatment of HCV in VA users ultimately met inclusion criteria. Most VA patients currently living with HCV infection were born between 1945 and 1965 and were infected with HCV between 1970 and 1990. To prevent HCV-related complications such as cirrhosis, hepatocellular carcinoma, and death, medical personnel must identify and treat HCV. However, antiviral therapy has historically been limited by medication side effects, contraindications, and patient acceptance. Although treatment initiation rates are higher in the VA than in the general United States, only 23% of VA HCV patients have received treatment and, of those, only a minority were cured. Recent development of more effective and tolerable antiviral agents represents a major pharmacological breakthrough. Eradication of HCV is theoretically possible for the majority of HCV patients for the first time, although new barriers, such as high drug costs, may limit future uptake.

epidemiology; hepatitis C virus; United States; veterans

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD-9, *International Classification of Diseases, Ninth Revision*; NHANES, National Health and Nutrition Examination Survey; SVR, sustained virological response; VA, Veterans Affairs.

INTRODUCTION

Hepatitis C virus (HCV) infection is the most common blood-borne pathogen in the United States, with an estimated 2.7 million chronically infected persons (1). Chronic HCV infection is approximately 2–3 times more common among veterans who receive care in the Veterans Affairs (VA) system than among the general US population (2). Furthermore, HCV-infected veterans are more likely to have additional risk factors that predispose to the development of cirrhosis, hepatocellular carcinoma (HCC), and liver failure. As a result, the impact of the HCV epidemic, which is only recently being recognized in the United States, has been even greater in the VA system. HCV infection is by far the predominant cause of cirrhosis, HCC, and liver failure among veterans and a major cause of overall mortality and morbidity. Furthermore, the prevalence and incidence of HCV-related cirrhosis and HCC have been increasing and are projected to continue to increase dramatically over the next 20 years.

After initial infection, HCV remains largely asymptomatic for 2–4 decades until it presents clinically with complications of cirrhosis, HCC, or liver failure. Therefore, diagnosis of HCV in the precirrhotic stages of disease requires screening. A significant proportion of persons infected with HCV remain undiagnosed both nationally and within the VA. Screening recommendations for HCV have recently been amended to include all persons born between 1945 and 1965 (3, 4) but have not yet been widely adopted nationally.

The goal of HCV antiviral treatment is to achieve viral cure, commonly called "sustained virological response" (SVR), defined as absence of HCV in the blood 6 months after the end of treatment. Until recently, treatment of HCV has been hampered by requiring injectable interferon-α which has substantial side effects, many contraindications, and low

response rates. This resulted in low treatment rates and even lower cure rates both nationally and in the VA system. Recently approved and upcoming direct antiviral agents against HCV have low adverse event rates and very high cure rates and represent a tremendous medical breakthrough. Direct acting antiviral agents could potentially greatly impact the HCV epidemic, although their high cost may be a barrier to widespread uptake. This systematic review will describe the epidemiology and treatment of HCV in the VA health-care system, placed in the context of HCV epidemiology in the United States as a whole.

METHODS

We identified published studies in English focusing on HCV in veterans by searching MEDLINE and Embase and using the following predefined criteria: adults aged >18 years and publication year from 1992 (when the HCV antibody test became widely available) through April 2014. The search terms related to this review were "veterans health" OR "veterans" OR "veteran" OR "United States Department of Veterans Affairs" AND "hepacivirus" OR "hepatitis c" OR "hepatitis c, chronic" OR "HCV" OR "hepatitis C" OR "hepatitis C virus." We also used reference lists from articles to identify other relevant studies.

Each study was screened for inclusion by both coauthors, and disagreements were resolved by discussion. We excluded work unrelated to the epidemiology of HCV prevalence and treatment in veterans, review articles, non–peer-reviewed work, practice guidelines, and studies based on case reports or case series. Patients coinfected with human immunodeficiency virus (HIV) and HCV differ considerably from HCV monoinfected patients in terms of antiviral treatment and prognosis. Therefore, studies focusing on coinfected patients were excluded unless they included an HCV monoinfected arm. Key papers describing the epidemiology of HCV in the wider US population were included to provide context, but the systematic review itself was limited to the VA.

Because of the heterogeneity of outcomes and analytical approaches among studies, we did not attempt to perform a meta-analysis and instead conducted a descriptive review of the literature. Descriptive data collected from each study included the study design, years of patient data involved, number of subjects, study location or data source, and a summary of outcomes.

RESULTS

Search findings

Outcomes of our search strategy are described in Figure 1. We located 28 unique articles (26 studies) that met our criteria describing HCV prevalence or treatment in US veterans, including 3 that were added on the basis of reference list review.

Characteristics of the HCV epidemic in the United States and relevance to the VA health-care system

The incidence of new HCV infections in the United States increased dramatically from 45,000 infections per year (95% confidence interval (CI): 0, 110,000) in the 1960s to 380,000 infections per year (95% CI: 250,000, 500,000) in the 1980s (5). This incidence declined sharply to about 38,000 new HCV infections per year in the 1990s and 17,000–19,000 infections per year after the year 2000 (6). This decline is putatively related to the widespread introduction of HCV serological testing between 1990 and 1992, which effectively eliminated HCV transmission via transfusion of blood products, and the institution of safer needle-using practices among injection drug users, driven by the HIV epidemic. Thus, the majority of HCV-infected persons currently living in the United States were born between 1945 and 1965 and were infected as young adults between 1970 and 1990 (3, 4). The epidemiology of HCV in the United States over the last 20 years and in the next 20 years will be dominated by this cohort of HCV-infected patients as they age over time and accumulate more years of chronic HCV infection. This cohort is in the process of moving through the various clinical phases of HCV, from infection to progressive fibrosis, cirrhosis, HCC, liver failure, and death.

The largest cohort of living veterans served during the Vietnam era, generally defined as 1964–1975. These Vietnam-era veterans are part of the baby boomer birth cohort (1945–1965), which has the highest prevalence of HCV infection. This overrepresentation of Vietnam-era veterans is important in understanding the high prevalence of HCV and the epidemics of HCV-related cirrhosis and HCC among VA users, as further described below.

The prevalence of HCV infection in the United States peaked in 2001 and has since been declining gradually because of the high number of deaths among HCV-infected patients and the low incidence of new infections (7). According to nationally representative data from the National Health and Nutrition Examination Survey (NHANES) studies, the prevalence of chronic HCV infection in the United States, defined by positive HCV RNA testing, was 1.2% (95% CI: 1.1, 1.4) or 2.7 million in 1988–1994 (8), 1.3% (95% CI: 1.1, 1.6) or 3.2 million in 1999–2002 (9), and 1% (95% CI: 0.8, 1.2) or 2.7 million in 2003–2010 (1). Because NHANES studies do not capture homeless and incarcerated persons, 16%–41% of whom are HCV infected (10), the true prevalence of HCV infection is substantially greater. Although the prevalence of HCV is declining in the United States nationally, the prevalence and incidence of HCV-related cirrhosis, HCC, and death will continue to rise until 2030 because of the lag time between infection and development of these clinical complications of HCV infection (7). HCV-related deaths have already exceeded HIV-related deaths in the United States since 2007 and are continuing to rise while HIV-related deaths are declining (11).

Screening for HCV infection in the VA health-care system

Since August 2012, the Centers for Disease Control and Prevention (CDC) has recommended one-time HCV screening for all persons born between 1945 and 1965 ("baby boomers") because this cohort includes 75% of all HCV-infected persons currently living in the United States (3, 4). Among 5.4 million persons who received VA care in 2011,

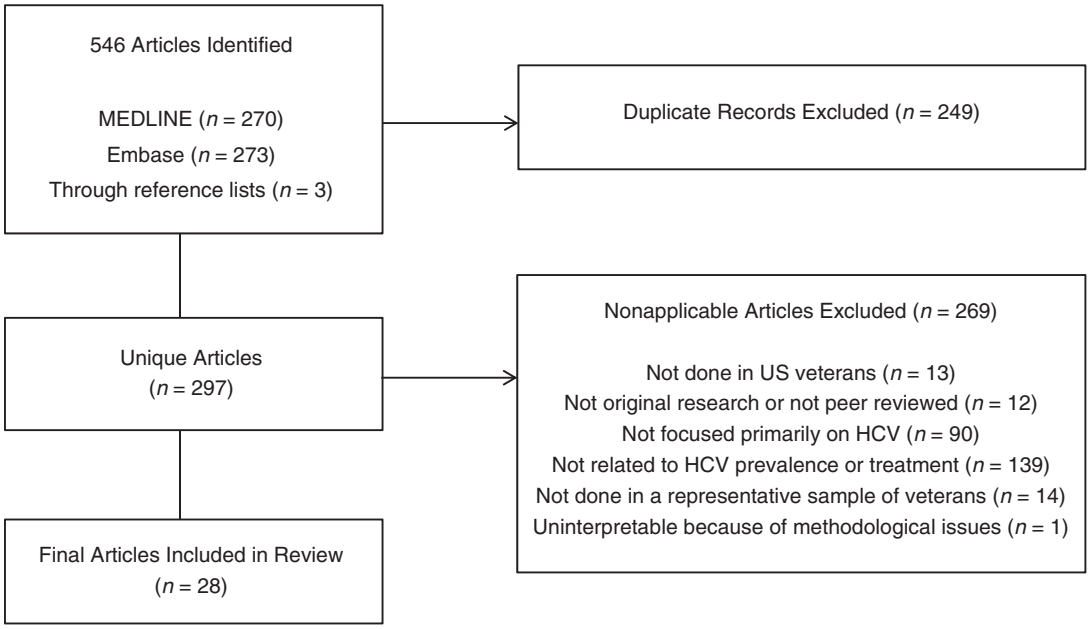

Figure 1. Article selection process. Articles were selected by using the search terms "veterans health" OR "veterans" OR "veteran" OR "United States Department of Veterans Affairs" AND "hepacivirus" OR "hepatitis c" OR "hepatitis c, chronic" OR "HCV" OR "hepatitis C" OR "hepatitis C virus," and the date range for studies included 1992 through April 2014. HCV, hepatitis C virus.

2.9 million (53%) had ever received screening for HCV in the VA system, including 63.5% of those born during the 1945–1965 period (12). Thus, even before the Centers for Disease Control and Prevention recommendation was made in 2012, the majority of baby boomers in VA care had already been screened for HCV. This was the result of previous screening efforts in the VA, such as hepatitis C "screening days" during which all veterans undergoing routine phlebotomy on a single day were tested for HCV (13) in addition to screening based on traditional risk factors. The VA has leveraged point-of-care clinical reminders to promote risk factor–based HCV screening for all new patients. These reminders direct the provider to offer HCV testing based on traditional risk factors, such as history of intravenous drug use, as well as service during the Vietnam era. However, the results of Backus et al. (12) suggest that 36.5% of baby boomers in VA care have not been screened for HCV (at least within the VA system) and should be targeted for future screening. One limitation of the HCV clinical reminder is that it only appears at the time of the patient's initial clinic visit, such that patients whose risk factors change or who decline screening the first time it is offered do not receive a subsequent reminder.

Prevalence of diagnosed HCV infection in the VA health-care system

A total of 5,598,829 veterans received VA health care in fiscal year 2012, up from 3,427,925 in fiscal year 2000 (14). The VA has accurate data on the number of patients who are already diagnosed with HCV infection, through the Hepatitis C Clinical Case Registry, which is overseen by the Population Health Group of the VA's Office of Public Health. As part of the Hepatitis C Clinical Case Registry, *International Classification of Diseases, Ninth Revision* (ICD-9), codes and laboratory results consistent with chronic HCV infection are automatically abstracted nationally (15). Specially trained Hepatitis C Clinical Case Registry coordinators at each facility then confirm that patients truly have HCV infection on the basis of presence of a positive HCV RNA test or documentation in chart notes and enter the patient into the Clinical Case Registry. The Hepatitis C Clinical Case Registry provides continually updated data on the number of patients known to be infected with HCV nationally together with critical clinical information such as demographics, HCV genotype, presence of cirrhosis, and receipt of antiviral treatment.

Data abstracted from the Hepatitis C Clinical Case Registry reports from 2009 to 2013 are shown in Table 1. Among 5,720,614 veterans in VA care in 2013, 174,302 (3.0%) had been diagnosed with chronic HCV infection. The numbers with diagnosed chronic HCV infection in care each year were similar between 2009 and 2013. Because not all patients in VA care have been tested for HCV, some patients remain undiagnosed. For example, out of 5,499,498 patients in VA care in 2011, 2,889,385 had been tested as of that year (12), and 180,498 were diagnosed with chronic HCV (6.2% of those tested or 3.3% of the entire population). Assuming a prevalence of HCV among VA users of ~4.1%, as estimated by Dominitz et al. (2), we would expect 225,479 patients to have chronic HCV out of 5,499,498 patients in care, suggesting that ~45,000 HCV-infected patients in VA care (20%) are not yet diagnosed.

Table 1. Prevalence of Diagnosed HCV Infection Among Veterans in VA Care and Major Complications of HCV, 2009–2013

Year	Veterans in VA Care, No.[a]	HCV Viremia, No.[b,c]	Deaths, No.	Cirrhosis, No.	% of HCV-Infected Patients With Cirrhosis	HCC, No.	% of HCV-Infected Patients With HCC
2013	5,720,614	174,302	7,812	29,578	17	4,916	2.8
2012	5,598,829	178,819	7,913	27,903	16	4,495	2.5
2011	5,499,498	180,498	7,268	25,804	14	3,870	2.1
2010	5,351,873	180,182	6,932	23,337	13	3,332	1.8
2009	5,139,285	177,974	6,687	20,971	12	2,756	1.5

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; VA, Veterans Affairs; VHA, Veterans Health Administration.

[a] Patients who received VHA care during that fiscal year (58).

[b] Patients who ever had a positive HCV RNA test, among patients who received VHA care that fiscal year (i.e., includes patients whose HCV infection might have been cured by treatment and also includes patients tested after the index year).

[c] L. Backus, VA Office of Public Health, Population Health Group, personal communication, 2014.

Interestingly, the number of HCV-positive patients in the United States was approximately 2.7 million during the time period 2003–2010 (1), of whom only an estimated 50% (or 1.35 million) had already been diagnosed (16). Therefore, approximately 13% (180,498/1,350,000) of all patients diagnosed with HCV infection in the United States received care within the VA health-care system in the single year 2011.

Prevalence of HCV infection in the VA health-care system

Early studies of anti-HCV antibody prevalence (which denotes past infection with HCV, with or without current infection) in the VA system reported estimates as high as 17%–35% (Table 2). However, these reports inflated the true prevalence of HCV among all VA users because they were based on selected patients who were undergoing phlebotomy for clinical indications (13, 17, 18) or on retrospective populations who happened to be tested for HCV (19). As a result, the Department of Veterans Affairs commissioned a nationwide epidemiologic study of HCV in 2001 specifically to determine the true prevalence of HCV in VA users and the underlying risk factors for infection. Using a 2-staged cluster sample, researchers found that 1,288 of 3,863 randomly selected veterans who received care at 20 VA facilities across the country from 1998 to 2000 completed a risk factor survey and underwent serological testing, of whom 4.0% tested positive for anti-HCV antibody (2). After adjustment for nonparticipation by use of information for nonparticipants available in VA databases, the prevalence of anti-HCV antibody among VA users was 5.4% (95% CI: 3.3, 7.5), of whom 75% were found to be positive for HCV RNA (which denotes chronic HCV infection).

The prevalence of anti-HCV antibody in the United States during a similar time period estimated by the NHANES 1999–2002 was 1.6% (95% CI: 1.3, 1.9) (9), which is 3 times lower than the prevalence in VA users. However, these estimates are not directly comparable. First, NHANES studies do not include homeless or incarcerated persons who have a higher prevalence of HCV and do not provide a method for adjustment for the high HCV prevalence in these groups. Second, VA users were almost exclusively men who have a

Table 2. Studies Estimating the Prevalence of Chronic HCV Infection in VA Users, 2000–2013

First Author, Year (Reference No.)	Participants, No.	Prospective or Retrospective	Selection of Participants (Random vs. Nonrandom)	Correction for Nonparticipation	Single or Multiple VA Facilities	Positive Anti-HCV Antibody[a]		Positive HCV RNA Viral Load[b]	
						%	95% CI	%	95% CI
Cheung, 2000 (19)	8,558	Retrospective	Nonrandom	No	Single	35			
Briggs, 2001 (17)	1,032	Prospective	Nonrandom	No	Single	17.7	17.2, 18.2	15.9	
Bräu, 2002 (18)	1,098	Prospective	Nonrandom	No	Multiple	10.6	8.7, 12.4	8.2	6.6, 9.8
Roselle, 2002 (13)	26,102	Prospective	Nonrandom	No	Multiple	6.6			
Dominitz, 2005 (2)	1,288	Prospective	Random	Yes	Multiple	5.4	3.3, 7.5	4.1	2.5, 5.6
Backus, 2013 (12)	2,889,385	Retrospective	Nonrandom	No	Multiple	8.4		6.2	

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; VA, Veterans Affairs.

[a] "Positive anti-HCV antibody" denotes exposure to HCV. About 75%–80% of patients with positive anti-HCV antibody have chronic HCV infection (evidenced by a positive HCV RNA viral load).

[b] "Positive HCV RNA viral load" denotes chronic HCV infection.

Table 3. Prevalence of Anti-HCV Antibody in VA Users and in the US Population Among Men of Comparable Age Groups, 1999–2003

Age by Population Type, Years	Anti-HCV Antibody Prevalence, %
VA users, 1999–2003 (2)	
35–54	11.5
55–74	3.7
NHANES-based estimate of US population, 1999–2002 (9)	
40–49	6.5
50–59	2.0
60–69	1.1

Abbreviations: HCV, hepatitis C virus; NHANES, National Health and Nutrition Examination Survey; VA, Veterans Affairs.

higher prevalence of HCV than women. Finally, NHANES participants were aged ≥6 years and reflected the age distribution of the US population. VA users included all adults and contained an overrepresentation of persons born from 1945 to 1965 who have the highest prevalence of HCV. Table 3 describes anti-HCV antibody prevalence estimates that have been reported in representative samples of VA users and the US population, limited to men and for comparable age groups. These estimates show that the prevalence in VA users was approximately double that in the US population.

Veterans who seek VA care represent a nonrandom subgroup of all veterans. An estimated 21.6 million veterans lived in the United States in 2011, of whom 5,499,498 (25.5%) received VA care (20). Many predictors of HCV infection are overrepresented among VA users compared with veterans who do not access VA health care. Indeed, 2 NHANES-based studies did not find an increased HCV prevalence in a representative sample of veterans compared with nonveterans (8, 9).

Traditional risk factors versus military exposures for HCV

The high prevalence of HCV among VA users can be explained to a large extent by the age and gender distribution of VA health-care users as outlined above and by exposure to "traditional" risk factors. Traditional risk factors include injection drug use, transfusion of blood products before 1992, intranasal cocaine use, male to male sex, and body tattoos. Number of sexual partners is also associated with HCV infection, but this is likely because of misclassification and incomplete adjustment for confounders, such as drug use, given that HCV is only very rarely transmitted sexually among heterosexual couples (transmission rate estimated as 1 per 190,000 sexual contacts in heterosexual, monogamous couples (21)). Additional characteristics that predict HCV infection due to confounding by other risk factors include incarceration, low income, low educational attainment, alcohol use, and marijuana use. Among randomly selected VA users tested for HCV, 78% of those testing positive for anti-HCV reported either transfusion before 1992 or injection drug use, while all had one or more of the broader risk factors listed above (2). In a study from the Palo Alto VA, 81% of 409 newly diagnosed HCV-infected patients were reported by their physicians to have a history of intravenous drug use, and an additional 2% had a history of blood transfusions (19).

It has been postulated that military-related exposures to HCV might contribute to the high prevalence of HCV among VA users. Such exposures potentially include the use of air injection for immunization ("air-gun injectors") and exposure to another person's blood in combat. One study reported that having a combat job as a medical worker was significantly associated with chronic HCV infection after adjustment for multiple potential confounders (adjusted odds ratio = 2.68, 95% CI: 1.25, 5.6) (17). However, a study that was specifically designed to determine whether military exposures were associated with HCV infection did not find an association between HCV infection and exposure to another person's blood in combat or ever receiving air injections (2). However, this study might have been underpowered to detect associations of low magnitude, as only 52 of 1,288 randomly selected VA users tested positive for anti-HCV antibody including only 39 who were HCV RNA positive.

HCV-infected Vietnam era veterans seen in non-VA facilities report very similar, "standard," non–military-related HCV risk factors as HCV-infected nonveterans seen in the same facilities (22). Furthermore, NHANES studies that are representative of the US population have not shown increased prevalence of HCV in persons who have served in the US military compared with those who have not, which also argues against military exposures per se being important risk factors for HCV infection (8, 9). The prevalence of anti-HCV antibody among 10,000 active duty personnel in 1997 was very low at 0.48%, while the annual incidence during military service was estimated from sequential samples to be 2 in 10,000 personnel (23). Although it is theoretically possible that air-gun injectors and exposure to blood in combat could have led to HCV transmission among Vietnam era veterans, this is almost impossible to prove, because serological tests for HCV did not become available until the 1990s and even today there is no serological marker of acute HCV infection, which is often asymptomatic. The weight of available evidence suggests that traditional, non–military-related exposures can account for the vast majority of HCV infections in VA users.

Characteristics of HCV-infected persons in the VA health-care system

On the basis of national VA Hepatitis C Clinical Case Registry reports, patients diagnosed with HCV infection in VA care in 2013 ($n = 174,302$) had a mean age of 59.7 years with 91% being between the ages of 50 and 69 (i.e., "baby boomers"), 97% were male, and 54% were white, 34% black or African American, and 6% Hispanic or Latino (Table 4). Among those whose HCV genotype was ascertained, 80% had genotype 1, 12% genotype 2, 7% genotype 3, and 1% genotype 4 infection. HIV coinfection was present in 2.9%. Psychiatric comorbidities including depression (60%), anxiety (37%), post–traumatic stress disorder (28%), bipolar disorder (13%), and schizophrenia (10%) were present in the majority of patients. A history of substance use disorders including alcohol (55%), cannabis (26%), stimulants (35%), opioids (22%), sedatives or anxiolytics (5%), and unspecified drug use (39%)

Table 4. Characteristics of HCV-Infected Persons in VA Care, 2013[a]

Characteristics	All Patients (n = 174,302), %
Age, Years	59.7[b]
<30	<1
30–39	1
40–49	3
50–59	42
60–69	49
70–79	3
>79	1
Male	97
Race	
White	54
Black or African American	34
Asian	<1
American Indian/Alaska Native	<1
Native Hawaiian/Pacific Islander	<1
Two or more races	<1
Unknown	9
Ethnicity	
Hispanic or Latino	6
Not Hispanic or Latino	89
Two or more	<1
Unknown or declined	5
HIV/HCV coinfected (n = 5,111)	2.9
Genotype (among those tested)	
1	80
2	12
3	7
4	1
5	0.02
6	0.03
No VA genotype available	23
Ever received antiviral agents	23
Cirrhosis or advanced liver disease[c]	17
Hepatocellular carcinoma[c]	2.8
Medical comorbidities	
Hypertension	68
Ischemic heart disease	17
Congestive heart failure	7
Diabetes mellitus, type 2	29
COPD	23
Asthma	7
Emphysema	3
Psychiatric comorbidities	
Bipolar disorder	13
Depression	60
Neuroses and anxiety states	37
Post–traumatic stress disorder	28
Any mental illness	69
Substance use disorders	
Alcohol use	55
Cannabis	26
Opioids	22
Stimulants	35
Tobacco use	66

Abbreviations: COPD, chronic obstructive pulmonary disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD-9, *International Classification of Diseases, Ninth Revision;* VA, Veterans Affairs.

[a] L. Backus, VA Office of Public Health, Population Health Group, personal communication, 2014.

[b] Presented as a mean value.

[c] A diagnosis of cirrhosis/advanced liver disease or hepatocellular carcinoma is defined by inpatient, problem list, and outpatient ICD-9 codes. One inpatient diagnosis code, 1 problem list code, or 2 outpatient diagnosis codes occurring on different dates associated with cirrhosis or advanced liver disease are required to count a veteran as having that condition.

Table continues

was also present in the majority of HCV-infected patients. Tobacco use disorder was present in 65%. Common medical comorbidities included hypertension (69%), dyslipidemia (43%), diabetes mellitus (28%), chronic obstructive pulmonary disease (22%), ischemic heart disease (17%), and chronic renal failure (9%). The high prevalence of substance use disorders and medical and psychiatric comorbidities among VA HCV-infected patients further complicates the management of their HCV infection.

Prevalence of cirrhosis and HCC in HCV-infected persons in the VA health-care system

Cirrhosis and HCC merit special attention because they are the pathways by which chronic HCV infection can lead to liver-related morbidity and mortality, typically several decades after HCV infection. Because the majority of HCV infections in the United States occurred between 1965 and 1990 (3, 4), a dramatic increase in the prevalence and incidence of cirrhosis and HCC has occurred since 2000 in both the VA and nationwide. Nationally, the total number of patients with HCV-related cirrhosis is expected to peak at 1 million in the year 2020 and decline thereafter (7). Cases of cirrhosis or HCC in VA care have been defined by the presence of validated inpatient or outpatient ICD-9 codes recorded by health-care providers. Kanwal et al. (24) reported that the prevalence of cirrhosis among patients in the VA with known HCV infection increased from 9% in 1996 to 18.5% in 2006, while the prevalence of HCC increased from 0.07% to 1.3%. Between 1996 and 2006, the absolute number of HCV-infected patients with cirrhosis increased from 2,061

to 23,294, and the number with HCC increased from 17 to 1,619.

Data from the VA Hepatitis C Clinical Case Registry indicate that the prevalences of cirrhosis and HCC have continued to increase between 2009 and 2013 (Table 1). Of note, Hepatitis C Clinical Case Registry data are not directly comparable to the data from Kanwal et al. (24) because of small differences in the diagnostic definitions of HCC and cirrhosis and mainly because of the large number of VA users diagnosed with HCV since 2006 as a result of screening efforts. The number of HCV-infected patients with cirrhosis continues to increase, from 20,971 (12% of patients with known HCV infection) in 2009 to 29,578 (17%) in 2013. A much more dramatic increase occurred in the prevalence of HCC from 2,756 (1.5%) in 2009 to 4,916 (2.8%) in 2013. The reported prevalence of cirrhosis in these reports almost certainly underestimates the true prevalence because of underdiagnosis of early cirrhosis. Antiviral treatment for HCV is critically important to preventing future cases of cirrhosis and HCC.

The evolution of HCV antiviral therapy

The first drug for HCV, the injectable cytokine interferon-α-2b, was approved by the US Food and Drug Administration in 1986. A breakthrough in HCV treatment occurred with the use of ribavirin in combination with interferon starting in 1998. A pegylated form of interferon was approved in 2001, which reduced the frequency of injections to once weekly by increasing the drug's half-life. All interferon compounds have many contraindications and side effects, including depression, hematological abnormalities, and flu-like symptoms that must be tolerated for up to 48 weeks of therapy. Pegylated interferon and ribavirin ("dual therapy") remained the standard of care for all HCV genotypes from 2001 until direct acting antiviral drugs were released in 2011.

In contrast with interferon, direct acting antiviral medications target the virus's replication machinery rather than stimulating the host's immune system. The first direct acting antivirals, boceprevir and telaprevir, were approved by the US Food and Drug Administration in 2011 for the treatment of genotype 1 HCV in combination with pegylated interferon and ribavirin. These 2 oral HCV serine protease inhibitors brought improved treatment efficacy along with significantly greater side effects, costs, drug–drug interactions, and inconvenience due to increased pill burden and rigid dosing schedules. In the VA, boceprevir costs significantly less than telaprevir ($17,812–32,022 vs. $41,388–45,948). The VA selected boceprevir as the formulary-preferred first generation protease inhibitor, although telaprevir is made available when specifically requested and justified by providers. There is no firm evidence that either of these 2 drugs is superior to the other as they have never been directly compared in head-to-head clinical trials.

A second group of direct acting antiviral medications entered the US market in late 2013, including the novel polymerase inhibitor, sofosbuvir, and the second-generation protease inhibitor, simeprevir. Sofosbuvir and simeprevir are both once daily oral medications with relatively few known side effects or drug interactions. Emerging regimens offer higher SVR rates in addition to shorter treatment duration and in many cases can be given without interferon.

Rates of antiviral treatment for HCV in the VA health care-system

As of 2013, 23% of HCV patients in VA care had ever received antiviral treatment (Table 5). This exceeds the 13% rate of HCV treatment in the United States based on the most recent data available from the NHANES 2003–2010 (16, 25). Even considering the difference in time periods between the NHANES and VA data, a significantly larger proportion of VA patients with HCV have received antiviral therapy. The VA's comparatively high treatment rate is particularly notable in light of the high burden of medical and psychiatric comorbidities that constitute relative or absolute contraindications to interferon-based treatment, including cirrhosis, depression, and substance use disorders (Table 4).

Eligibility for interferon-based antiviral treatment

HCV treatment eligibility is a complex decision, particularly among patients who must contend with significant physical and psychiatric side effects from interferon. Nine large studies (10 articles) examined antiviral treatment using dual therapy in VA patients. The 8 articles describing rates of antiviral treatment initiation are summarized in Table 6. Contraindications to interferon were present in 48%–58% (26–28). In a prospective study of 4,084 VA users, nearly a fourth (23.8%) of those considered to meet minimum eligibility criteria for interferon declined it when offered (28). Top reasons for declining treatment included waiting for better therapies (50.3%), side effect concerns (21.6%), issues with complying with the regimen (2.2%), and other unspecified reasons (22.6%) (28). The same prospective study found that ongoing substance abuse,

Table 5. Studies of Receipt of Antiviral Treatment for HCV Among VA Patients, 2009–2013

Year	Veterans in VHA Care, No.[a]	In Care With HCV Viremia, No.[b,c]	Ever Received HCV Antiviral Treatments	
			No.	%
2013	5,720,614	174,302	39,388	23
2012	5,598,829	173,416	38,860	22
2011	5,499,498	170,119	36,898	22
2010	5,351,873	165,005	35,841	22
2009	5,139,285	156,725	33,981	22

Abbreviations: HCV, hepatitis C virus; VA, Veterans Affairs; VHA, Veterans Health Administration.

[a] Includes patients who received VHA care during that fiscal year (58).

[b] Patients who ever had a positive HCV RNA test, among patients who received VHA care that fiscal year (i.e., includes patients whose HCV infection might have been cured by treatment. Also includes patients tested after the index year).

[c] L. Backus, VA Office of Public Health, Population Health Group, personal communication, 2014.

Table 6. Studies of HCV Antiviral Treatment Initiation Rates in VA Patients, 2005–2012

First Author, Year (Reference No.)	Study Design	Sample Size	Time Period	Data Source	Treatment Initiation Rate, %
Bini, 2005 (28)	Prospective cohort	4,084	1999–2000	Standardized data collection	17.6 overall
Tsui, 2008 (31)	Prospective cohort	4,084	1999–2000	Standardized data collection	10 among those >60 years of age
Butt, 2007 (30)	Retrospective cohort	113,927	1999–2003	National VA Patient Care Database	11.8 overall
Kanwal, 2007 (33)	Retrospective cohort	14,275 (5,701 treatment eligible)	2000–2005	VA Southern California Network Data Warehouse	15.7 among treatment eligible
Rousseau, 2008 (32)	Retrospective cohort	4,236	2000–2005	Northwest Regional VA Data Warehouse	12.6 overall
Kramer, 2011 (29)	Retrospective cohort	29,695	2003–2004	Hepatitis C Clinical Case Registry	14.2 overall
Butt, 2011 (27)	Retrospective cohort	27,452 (8,906 treatment eligible)	1998–2003	ERCHIVES	23 among treatment eligible
Kanwal, 2012 (42)	Retrospective cohort	34,749	2002–2006	Hepatitis C Clinical Case Registry	17.9 overall

Abbreviations: ERCHIVES, Electronically Retrieved Cohort of HCV-Infected Veterans; HCV, hepatitis C virus; VA, Veterans Affairs.

comorbid medical disease, psychiatric disease, and advanced liver disease were the strongest predictors of not being considered a treatment candidate (28). Contraindications to treatment and patient refusal clearly contribute heavily to the low rates of interferon-based HCV treatment in VA patients.

Predictors of HCV treatment initiation with interferon

Independent negative predictors of HCV treatment initiation in VA patients include nonwhite race, older age, male sex, current substance use disorder, HCV genotype 1 or 4, and comorbid medical or psychiatric illness (29–32). Positive predictors of treatment include high baseline hemoglobin levels, cirrhosis, and persistently high liver enzyme levels (29). Using national administrative data, Kramer et al. (29) examined the variation in treatment rates among VA facilities and found that patient-level factors, such as those just described, accounted for 15% of the variation in treatment as opposed to 4% for both facility and provider-level factors, with evaluation by a specialist being the strongest overall predictor of starting therapy. A large portion of intrafacility variation remained unaccounted for in this analysis, with patient preference, unrecorded contraindications, or inappropriate nontreatment presumably making up the difference. A smaller regional VA study ($n = 5,701$) reported that patients evaluated by less-experienced providers were 77% less likely to receive treatment than those evaluated by specialists, and it found that provider-level factors accounted for 25% of the variability in treatment rates across the 5 facilities in the analysis (33). One national study reported that veterans were significantly more likely to receive treatment if seen in a facility with a dedicated HCV clinic, especially if associated with gastroenterology, or offering >13 half-days of HCV clinic per facility per week (34). In addition to patient-level comorbidities and individual willingness to undergo treatment, variable access to HCV specialists has had an important impact on availability of treatment.

HCV treatment outcomes with pegylated interferon and ribavirin in the VA

The VA's large population and comprehensive electronic medical record system make it ideal for studying real-world HCV treatment outcomes. Eight large retrospective cohort studies and 1 prospective study have examined treatment outcomes for pegylated interferon and ribavirin; the 8 studies that reported SVR are summarized in Table 7. Overall SVR rates using pegylated interferon and ribavirin ranged from 20% to 23.6% in patients infected with genotype 1 and from 43% to 52% in patients infected with genotypes 2 and 3, with wide variation reported when SVR was assessed in subgroups, such as those with favorable early treatment response. Overall rates of SVR tend to be lower in VA-based populations than in clinical trials for dual therapy, which reported rates of 52% in genotype 1 and 80% in genotypes 2 and 3 (35–37).

Premature treatment discontinuation likely accounts for a large share of the low SVR rates observed in VA patients. Most VA-based studies of dual therapy with pegylated interferon and ribavirin report that at least half the patients who started treatment did not complete it, either because of deliberate discontinuation in the setting of lack of virological response or because of unplanned discontinuation most commonly due to intolerable side effects or adverse drug reactions (26, 38–42). In general, studies agree that higher levels of patient medication adherence were associated with greater likelihood of SVR (38–40). Low SVR is also associated with black race, age, and patient comorbidities such as cirrhosis and diabetes, which are more prevalent in the VA HCV population compared with clinical trials.

The VA population is enriched in negative predictors of SVR, making adequate monitoring and pretreatment preparation important to bolstering outcomes. Three VA studies have investigated systems-based predictors of treatment results. Several studies report a link between treatment outcomes and treatment center volume or provider experience (40–42). In

Table 7. Studies of Outcomes of HCV Antiviral Therapy With Pegylated Interferon and Ribavirin in VA Users, 2005–2012

First Author, Year (Reference No.)	Study Design	Sample Size	Time Period	Data Source	Overall Proportion Completing Treatment, %[a]	SVR Reported in Subgroup vs. Overall	SVR, %		
							Genotype 1	Genotype 2	Genotype 3
Cheung, 2005 (59)	Prospective cross-sectional	2,931	1999–2000	Standardized patient data collection	60.2 (Latinos) 71.1 (Caucasians)	Subgroup[b]	10.2 (Latinos) 14.6 (Caucasians)	17.7 (Latinos) 38.4 (Caucasians)	
Backus, 2007 (40)	Retrospective cohort	5,944	Post-2003	Hepatitis C Clinical Case Registry	32 (genotype 1) 66 (genotype 2) 59 (genotype 3)	Overall	20	52	43
Beste, 2010 (39)	Retrospective cohort	11,019	2002–2007	Hepatitis C Clinical Case Registry	53 (genotype 1)	N/R	N/R	N/R	N/R
Butt, 2010 (41)	Retrospective cohort	16,043	1998–2003	ERCHIVES	22.5	N/R	N/R	N/R	N/R
Lo Re, 2011 (38)	Retrospective cohort	5,706	2003–2006	Hepatitis C Clinical Case Registry	42.6[c]	Subgroup[d]	47	69	
Hwang, 2012 (60)	Retrospective cohort	3,509	2007–2008	Hepatitis C Clinical Case Registry	N/R	Subgroup[e]	18 (no RVR) 52 (RVR)	39 (no RVR) 71 (RVR)	40 (no RVR) 60 (RVR)
Kanwal, 2012 (42)	Retrospective cohort	6,224	2002–2006	Hepatitis C Clinical Case Registry	N/R	Overall	32		
Kramer, 2012 (26)	Retrospective cohort	11,479	2000–2005	Hepatitis C Clinical Case Registry	47.7 (genotype 1 or 4) 75.2 (genotype 2 or 3)	Overall	23.6	50.6	

Abbreviations: ERCHIVES, Electronically Retrieved Cohort of HCV-Infected Veterans; HCV, hepatitis C virus; N/R, not reported; RVR, rapid virological response (i.e., undetectable viral load by week 4 of antiviral therapy); SVR, sustained virological response; VA, Veterans Affairs.

[a] Treatment "completion" defined by finishing >80% of recommended duration.

[b] SVR reported for Latinos versus non-Latinos.

[c] Completed 37–48 weeks.

[d] SVR reported for patients who achieved early virological response, defined as >100-fold decrease in viral load by week 12 of treatment.

[e] SVR reported for patients with respect to RVR, defined as undetectable viral load by week 4 of treatment.

Table 8. Studies of Outcomes of HCV Antiviral Therapy With Pegylated Interferon, Ribavirin, and Boceprevir or Telaprevir in VA Users, 2013

First Author, Year (Reference No.)	Study Design	Sample Size	Time Period	Data Source	Boceprevir, % SVR	Telaprevir, % SVR
Ioannou, 2014 (43)	Retrospective cohort	759 (telaprevir) 3,696 (boceprevir)	June 2011–February 2013	VA Corporate Data Warehouse	52.2	47.3
Belperio, 2013 (61)	Retrospective cohort	198 (telaprevir) 661 (boceprevir)	June–December 2011	Hepatitis C Clinical Case Registry	50	52
Backus, 2014 (44)	Retrospective cohort	198 (telaprevir) 661 (boceprevir)	June–December 2011	Hepatitis C Clinical Case Registry	50	52

Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; VA, Veterans Affairs.

support of the notion that careful pretreatment preparation facilitates success, one study of 6,224 HCV patients treated between 2003 and 2006 observed that adherence to pretreatment quality measures for HCV, such as genotype testing, evaluation for relevant comorbid conditions, and specialty evaluation, was independently associated with both treatment completion and SVR (42).

Treatment outcomes with pegylated interferon, ribavirin, and boceprevir or telaprevir

More than 80% of VA patients treated with first generation protease inhibitors between 2011 and 2013 received boceprevir, while the remainder received telaprevir (43). The SVR rate in VA patients with HCV genotype 1 treated with either boceprevir or telaprevir was approximately 50% (43, 44), substantially below rates of 66%–79% reported in randomized controlled trials (Table 8) (45–48). Similar SVR rates were reported for boceprevir and telaprevir, and it is unclear whether any clinically relevant differences in SVR rates exist after adjustment for important confounders. As with dual therapy, adverse baseline patient characteristics and early treatment discontinuation likely explain many of the lower SVR rates observed in VA practice compared with clinical trials for boceprevir and telaprevir. For example, a higher proportion of treated VA patients had cirrhosis (34%), diabetes (34%), baseline anemia (7.1%), baseline platelet count <100,000/μL (9.9%), or prior null response to treatment (14%) compared with clinical trials (43). Early treatment discontinuation was extremely common: Among VA patients who were supposed to complete 48-week regimens, only 35% of boceprevir-treated and 34% of telaprevir-treated patients completed >44 weeks (43).

Long-term outcomes after HCV antiviral treatment

The ultimate purpose of HCV treatment is to reduce morbidity and mortality from cirrhosis, HCC, and liver failure as well as extrahepatic complications of HCV. Two studies of VA patients with HCV demonstrated lower all-cause mortality among those who achieved successful viral eradication compared with those who were not treated or who were unsuccessfully treated (49, 50). These results (Table 9) are consistent with those from community-based studies showing improved survival with successful antiviral treatment, and they lend weight to the effort to increase the uptake of antiviral therapies in VA patients (51–53).

DISCUSSION

Approximately 175,000 patients with diagnosed HCV infection are currently in VA care, plus an estimated 45,000 additional patients with as yet undiagnosed infection. Large proportions of HCV patients have already developed cirrhosis or HCC, and the prevalence and incidence of these complications are projected to increase dramatically in the next

Table 9. Studies of Long-Term Outcomes in VA Users After HCV Antiviral Treatment, 2009–2011

First Author, Year (Reference No.)	Study Design	Sample Size	Study Population	Data Source	Median Follow-up Duration, Years	Risk of Death	
						HR	95% CI
Butt, 2009 (50)	Matched survival analysis	34,480 pairs	Positive HCV antibody or detectable HCV RNA during 2001–2006 matched with uninfected controls	ERCHIVES	~3	0.41[a]	0.27, 0.64
Backus, 2011 (49)	Retrospective cohort	22,942	Genotype 1, 2, or 3 HCV treated between 2001 and 2007	Hepatitis C Clinical Case Registry	3.8	0.70 (genotype 1)[b] 0.64 (genotype 2)[b] 0.51 (genotype 3)[b]	0.59, 0.83 0.46, 0.88 0.35, 0.73

Abbreviations: CI, confidence interval; ERCHIVES, Electronically Retrieved Cohort of HCV-Infected Veterans; HCV, hepatitis C virus; HR, hazard ratio; SVR, sustained virological response; VA, Veterans Affairs.

[a] Treated vs. untreated patients.

[b] Treated patients with SVR vs. without SVR.

10–20 years. The VA faces a major test in treating the HCV-infected patients in its care before they develop irreversible complications of chronic liver disease. Until recently, the only available HCV therapies were based on the drug interferon-α, which has low effectiveness, many side effects, and frequent contraindications. As of 2013, 23% of HCV patients in the VA had previously attempted antiviral treatment, but the majority of these were not cured. Historically, the main limitations to successful antiviral treatment in the VA, as well as other health-care organizations, included patient eligibility, acceptance of treatment, and low rates of SVR among the minority that did attempt it.

Despite the fact that a large majority of its HCV patients have not yet been cured, the VA has demonstrated relative success in treating a higher proportion of its patients than the US health-care system as a whole. This achievement is made more remarkable by the presence of very high rates of medical and psychiatric comorbidities within the HCV cohort that typically present obstacles to treatment initiation. For example, up to 58% of VA patients have contraindications to interferon (26–28), and of the eligible patients, nearly a quarter decline interferon (28).

Although not unique to the VA, access to specialty care has been recognized as another major barrier to HCV treatment in several VA-based studies. The VA's efforts to expand treatment have included a 3-year, $49.5 million telemedicine program to support primary care providers in delivering specialty services, including HCV treatment, to VA patients residing outside the catchment of tertiary centers. This initiative was based on pioneering work in the private sector demonstrating that HCV treatment delivered by primary care providers with specialty mentorship can achieve SVR outcomes at least as high those in tertiary settings (54). Telemedicine-supported HCV treatment is now available in much of the VA system.

Despite the VA's strides in providing HCV treatment to a comparatively large subset of patients, VA populations have experienced lower treatment success rates compared with those from published clinical trials. This phenomenon is predominantly explained by adverse patient-level treatment characteristics and by high rates of early treatment discontinuation. Recent US Food and Drug Administration approval of highly effective direct antiviral agents (sofosbuvir and simeprevir) and the expected introduction of many additional HCV drugs in 2014 and 2015 have completely changed the treatment landscape. Depending on pretreatment characteristics (e.g., prior nonresponse to therapy, viral subtype), SVR rates in clinical trials of sofosbuvir-based regimens are reported up to 92% for genotype 1 patients, 97% for genotype 2, and 96% for genotype 4 (55). Genotype 3 patients can achieve an SVR rate up to 94% but require 24 weeks of sofosbuvir-based therapy (56). For the first time in history, antiviral treatment and eradication of HCV are theoretically possible for the majority of HCV-infected patients.

Unfortunately, a new barrier to HCV treatment has emerged: the cost of the new antiviral agents. The approximate retail price of a 12-week course of sofosbuvir is $84,000 (or $1,000 per pill) and $66,360 for simeprevir, while some patients must receive both drugs simultaneously, although the VA has negotiated somewhat reduced prices (57). These costs do not include the expenses of additional medications, clinic visits, or laboratory tests. At most VA medical centers, treating all HCV-infected patients in their care would overwhelm the entire annual pharmacy budget. While the costs of antiviral agents remain prohibitively high such that only a small minority of HCV patients can initially be treated, prioritizing patients for antiviral treatment will likely remain an unfortunate necessity in all health-care systems. An important nuance in such prioritization strategies, as well as in everyday clinical practice, is the difficulty of accurately determining the point at which liver disease becomes "too advanced" such that eradication of HCV is unlikely to prevent or reduce the incidence of decompensated liver disease or HCC. The optimal strategy for prioritizing HCV patients for treatment is under intense debate within and outside the VA.

The incidence of cirrhosis, HCC, and related mortality is rising dramatically as baby boomers infected between 1970 and 1990 accumulate more years of chronic HCV infection. The promise of new, highly effective, and well-tolerated antiviral agents can be realized if a high proportion, or ideally all, of patients with HCV infection receive antiviral treatment before they develop irreversible complications of chronic liver disease. This can be achieved only if antiviral agents become more affordable and if significantly greater resources are allocated to antiviral treatment in the near future. Further study will be needed to determine the impact of newer antiviral drugs and their costs on treatment and outcomes for VA patients with HCV.

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