Dear Colleagues,

It is my pleasure to present the inaugural issue of the Gilead Hepatitis C Trends Report, which offers a thorough assessment of the current and future hepatitis C virus (HCV) market from the payer and healthcare provider perspectives. This report was developed through an intensive editorial process that synthesized quantitative study results, literature research findings, and market expert perspectives.

The management of HCV currently is a topic of intense focus and has been ranked as a leading priority by many managed care organizations (MCOs). The objectives of this first edition of the Hepatitis C Trends Report are to enhance market understanding of the HCV disease landscape and to assess screening, diagnosis, and management trends so as to foster communication and collaboration among payers and providers.

The report is divided into 2 sections:

1. An overview and analysis of HCV disease and management trends from the available literature

2. Results of an online survey of healthcare providers and managed care professionals comparing their perspectives and practices in HCV management with trends in the literature, with expert analysis from our Editorial Board to illuminate the reasons and motivations behind current attitudes

As Editorial Board member Deborah Reissman, PharmD, Director of Pharmacy, Sharp Community Medical Group notes, “The survey highlighted that many people do not know what their actual HCV prevalence is, how many total patients they have, how many patients they have successfully treated, or how many patients are being deferred.” It is our hope that by illustrating similarities and differences in stakeholder perceptions of these and other aspects of HCV management, the Gilead Hepatitis C Trends Report will be a valuable resource as we all work towards the common goal of helping patients with HCV.

Sincerely,

Coy Stout
Vice President, Managed Markets
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Executive Summary

Introduction

The United States (US) Department of Health and Human Services calls viral hepatitis a “silent epidemic.” Prevalence estimates for chronic hepatitis C virus (HCV) infection in the US vary from 2.7 million to as high as 7.1 million, but only about half of these individuals are aware they are infected. Chronic HCV infection places a substantial burden on individuals and the healthcare system in terms of morbidity and costs, which increase as associated liver disease progresses. Based on the years of peak US incidence, many people with HCV likely have been infected for decades and are at increased risk of progressing to advanced liver fibrosis or cirrhosis, the latter of which is estimated to occur in >40% of persons who have had HCV infection for 30 years. HCV is challenging to identify due to its chronicity and largely nonspecific symptoms (eg, abdominal discomfort, nausea, fatigue). Management also is complicated by comorbidities that render a high population of patients ineligible for certain HCV treatment options. The rapid evolution in HCV management has helped to focus new attention on the impact of infection in the US population. The past 3 years have witnessed major changes in available diagnostic and treatment modalities, and in screening and treatment recommendations. New screening guidelines, for example, now target the baby boomer birth cohort (the age group with the highest HCV prevalence), and direct-acting antiviral therapies (DAAs) have been introduced to the market. As a result, the number of patients being identified with and treated for HCV infection in the commercially-insured population is expected to steadily increase in the short term before leveling off. Treatment with antiviral therapy can result in virologic cure, and curing patients of HCV infection early enough in the course of disease can prevent progression to cirrhosis or to hepatic decompensation and the subsequent need for liver transplantation. Antiviral therapy also mitigates the cost burden of HCV infection. Barriers to increasing HCV treatment rates remain, however; these include issues with screening implementation, linkage to care, and access and referral to experienced specialists.

More than ever, managed care organizations (MCOs) are looking for guidance to weigh the benefits of therapy in terms of future cost offsets, to determine the cost effectiveness of regimens and to help them make crucial HCV treatment coverage decisions. Several recent reports, including those from Milliman, the California Technology Assessment Forum and Institute for Clinical Economic Review, the California Healthcare Institute, and Oregon Health & Science University have been produced in the past 2 years. These reports provide analyses of the value or cost impact of specific new therapies, the validity of new treatment recommendations, and the potential effect of new screening recommendations and increased treatment rates on the HCV landscape in general or for specific market segments. Produced by a variety of stakeholders, these reports present conflicting findings and viewpoints concerning the impact of current trends in the HCV marketplace. Interestingly, significant differences also exist between provider and payer perspectives on the HCV patient population and evolving treatment landscape. The Gilead Hepatitis C Trends Report is designed to provide insights into US payer and healthcare provider perspectives on the current and future HCV marketplace. These insights are discussed in the context of existing clinical and health outcomes literature. The report is intended for MCO decision makers and healthcare professionals who have a special interest in understanding current trends in HCV management and in helping patients with HCV. Issues such as HCV epidemiology, screening, diagnosis, disease burden, and management trends are addressed in this report. The Hepatitis C Trends Report is comprised of 2 main data sources:

- A comprehensive review of data concerning HCV trends from studies conducted in US populations, meta-analyses, US population-based models, screening and treatment guidelines/guidance, and US government publications
- An online market research survey that polled a cohort of healthcare providers and managed care professionals familiar with HCV about their perspectives and practices in HCV management. This survey was conducted on an unaided basis, and may reflect prevailing impressions and understanding of HCV, along with the stakeholders’ underlying approach to managing the disease. More information on the study design and limitations can be found in the following section (p. 26) and in the Appendix (p. 60).
Top-line Trends

HCV Prevalence and Diagnosis Rates

- Payer survey respondents estimated a 10% prevalence of HCV in their members. This rate is considerably higher than prevalence estimates from the Centers for Disease Control and Prevention (CDC) and other data sources (1%-2%).\(^\text{2,3,27}\) However, 31% of payers said they were unaware or unsure of this rate.

- Of healthcare providers surveyed, 68% reported the number of HCV patients they manage has increased over the past 2 years. In comparison, although more payers (38%) reported the prevalence of HCV diagnoses has increased in their plans/organizations over the past 2 years, 33% reported no change, and 29% said they did not know or weren’t sure.

- Healthcare providers projected the number of patients with HCV they manage per month would grow by approximately 12% in 2015 and 16% in 2016. In contrast, payers projected the number of members with HCV managed by their plans/organizations would remain flat in 2015 and grow 3% in 2016.
  - Payer estimates were impacted, in part, by responses from those in the corrections market, who estimate a 19% decrease in HCV diagnoses in 2015 and a 24% decrease in 2016. Payers affiliated with other market segments estimate minimal to modest growth in 2015 (1%-6%) and modest to moderate growth in 2016 (4%-13%).

- Payers estimated about 15% of individuals with HCV remain undiagnosed, whereas healthcare providers estimated 42%. In comparison, available data indicate 50% of individuals with HCV in the US are unaware they are infected.\(^\text{4}\)

- Of the healthcare providers surveyed, 36% said the percentage of undiagnosed HCV patients has decreased over the past 2 years, mainly because of increased screening and awareness. Only 8% of payers thought this percentage had decreased.

HCV Infection and Disease Characteristics

- Healthcare providers surveyed estimated 67% of their patients with HCV infection had genotype (GT) 1, which is slightly under the 70%-78% GT 1 HCV US prevalence rates reported in the literature.\(^\text{28-30}\) Among payer respondents, 40% indicated they were unsure of genotype distribution among their members, indicating a potential knowledge gap.

- Twenty-two percent of healthcare provider survey respondents estimated the average duration of HCV infection in their patients to be >20 years; 31% estimated the average duration of infection for their HCV patients was >10 but <20 years. In contrast, only 4% and 17% of payer respondents estimated the average duration of HCV infection in their members was >20 years or >10 but <20 years, respectively.

- Healthcare providers estimated that 23% of their HCV patients had no fibrosis (F0), 24% had mild fibrosis (F1), 18% had moderate fibrosis (F2), and 27% had severe fibrosis (F3) or cirrhosis (F4). Twenty-three percent of providers reported the percentage of HCV patients with F4 has increased over the past 2 years.

- The top 2 factors healthcare providers cited as contributing to a more rapid progression to HCV-associated cirrhosis were human immunodeficiency virus (HIV)-1 coinfection (75%) and duration of HCV infection (68%). Other contributing factors were high body mass index (BMI; 50%), African-American race (42%), older age at time of infection (39%), and male gender (32%).

- Perhaps because participants responded to survey questions unaided, payers were less sure of answers to questions concerning the burden of HCV in their members. Among payers, 42%-63% indicated they did not know/were unaware of the severity of fibrosis or the change in rate of progression to cirrhosis in the past 2 years among their members, as well as the proportion of members with HCV who will eventually require treatment for cirrhosis and other liver-related complications.

- An analysis of data from the National Health and Nutrition Examination Survey (NHANES) found chronic HCV was an independent risk factor for insulin resistance, hypertension, and congestive heart failure.\(^\text{31}\) The most common comorbidities in HCV patients noted by the surveyed healthcare providers were depression (27%), steatosis (19%), diabetes (18%), anemia (16%), and cardiovascular disease (16%).
  - Payer respondents listed the following as the top comorbidities among their members with HCV: diabetes (20%); depression (18%); cardiovascular disease (17%); and chronic hepatitis B infection (13%).
Top-line Trends (cont.)

Screening and Diagnosis Process

• Among healthcare providers, only 8% said they had not changed their HCV screening practices. Sixty-one percent had increased risk-based screening, and 59% had increased baby boomer birth cohort–based screening.

• Twenty-one percent of payers said they had not implemented any programs to increase HCV diagnosis rates at this time.

• Of healthcare providers surveyed, 80% reported they use lab-based antibody tests followed by tests confirming active HCV viremia to screen patients; 83% of payer respondents reported their organizations covered enzyme immunoassays for HCV screening. Only 22% of provider respondents said they used the HCV rapid antibody test, a modality that 55% of payer respondents reported was covered by their organizations.

• Although biopsy continues to be used by the majority of healthcare providers to diagnose liver disease severity (81%) or determine HCV treatment course (55%), 72% said they expect use of transient elastography to increase over the next 2 years.

• Half (50%) or more of payer groups said their organizations required lab-based HCV antibody testing, HCV genotype testing, and liver function tests (LFTs) for treatment initiation in their members. Only 27% and 17% of payer respondents said their plans required liver biopsy or transient elastography, respectively.

HCV Treatment Trends

• About half (52%) of payers responded that once HCV antiviral therapy has been initiated, on-treatment monitoring is required for therapy continuation. Twenty-nine percent said they required no on-treatment monitoring, and another 19% were unsure.

• Payers and providers who participated in the market research survey reported considerably higher treatment rates for HCV than seen in the meta-analysis by Yehia and colleagues (16%).

  – Payers estimated 47% of their members with HCV currently are being treated.

  – Healthcare providers estimated they are currently treating a similar proportion—41%—of patients.

• Healthcare providers estimated that 47% of their patients with F4 (cirrhosis) and 52% of their patients with F3 (severe fibrosis) are being treated today.

• Over half (54%) of healthcare providers anticipated the proportion of HCV patients with deferred treatment will decrease over the next 2 years.

• When asked to rank factors likely to have the greatest impact on HCV management over the next few years by assigning them a point value, healthcare providers assigned 50 out of 100 points to treatment attributes (eg, efficacy, tolerability, duration), whereas payers assigned 40 out of 100 points to this category of factors.

  – Payers considered environmental factors (eg, increased screening and treatment rates) to be slightly more important influencers on future management trends than treatment attributes, assigning the former 43 out of 100 points and the latter 40 out of 100 points, on average.

  – Healthcare providers assigned an average of only 37 out of 100 points to environmental factors, the most important of which were significant increases in rates of HCV screening (8.5 out of 100 points) and treatment (7 out of 100 points).

Cost Considerations

• Forty-six percent of payers reported HCV regimen cost-effectiveness has increased in importance over the past 2 years.

  – However, 75% of payers either said their organizations had not conducted cost-effectiveness comparisons of HCV antiviral regimens or did not know if they had.

• Fifty-two percent of payers said their organizations had plans to evaluate HCV regimens based on cost-effectiveness.

• Sixty percent of payers indicated “total cost (pharmacy + medical)/sustained virologic response (SVR)” was one of their top 3 relevant measurements of HCV regimen cost-effectiveness.

  – However, only 38% of respondents reported their plan/organization had the data capability to capture the total number of members with HCV who achieved SVR with treatment.
Top-line Trends (cont.)

Special Populations of Focus: Corrections and Veterans

• Healthcare providers who practiced in a Veterans Health Administration (VHA) setting said 75% of their patients had GT 1 infection

• VHA healthcare providers indicated they see patients they are monitoring but not yet treating 3 times per year, compared with 7 times per year for those who are receiving treatment. In comparison, non-VHA providers monitored patients who are not being treated 6 times each year and saw patients who are being treated 12 times per year

• VHA respondents estimated that only 21% of their HCV patients are actively being treated

• Payers whose organizations manage HCV care in corrections populations indicated disease severity was the most common criterion cited for HCV treatment authorization (50%), followed by duration of stay (ie, incarceration; 33%), and member contract or commitment to treatment (33%)

• Half (50%) of these payers indicated disease progression assessment was their approach to managing inmates with HCV for whom treatment was being deferred

• Half (50%) did not know or were unsure of their plan for discharging inmates with HCV for whom treatment had been deferred

Future issues of the Gilead Hepatitis C Trends Report will track how healthcare provider and payer perceptions of HCV burden, diagnosis, and management change over time, and will also examine remaining gaps in HCV knowledge.
Current Hepatitis C Virus (HCV) Landscape: United States (US) Trends in Disease Burden, Screening, and Treatment

Introduction
The management of HCV is rapidly evolving. The past 3 years have seen the introduction of new recommendations for screening approaches, new antiviral therapies, and multiple new management guidelines. Research and information concerning this infectious disease also has expanded considerably in recent years. In this decade alone, >13,000 articles, including >1000 clinical trials, have been published (PubMed searches). To provide context, identify evidence gaps, and facilitate comparison with the physician and payer HCV Assessment Survey findings, this section of the Gilead Hepatitis C Trends Report summarizes the most recent data available in the literature. Included are studies and analyses, guideline recommendations, and publications from US health authorities (and other sources) concerning trends in HCV epidemiology, disease burden, screening/diagnosis, and treatment in the US, with a particular focus on research available since 2010.

What is evident from this review is that knowledge gaps remain in key areas of HCV management that help to illuminate some of the primary research findings presented in this report. In addition, emerging data on cost-effectiveness of HCV screening approaches and treatment, as well as factors used to prioritize patients for treatment, are emerging issues with the potential to profoundly impact chronic hepatitis C (CHC) management practices. Although data support the substantial impact that increased screening and treatment rates, as well as increased rates of sustained virologic response (SVR) could have on reducing the clinical and cost burden of CHC, balancing resource constraints against these anticipated benefits remains a challenge.

CHC Epidemiology and Disease Burden
The estimated prevalence of HCV in the US ranges from 2.7-3.2 million persons, within estimates from the National Health and Nutrition Examination Survey (NHANES), to between 5.2 and 7.1 million individuals when including populations known to have a higher risk of HCV prevalence, such as the incarcerated and veterans populations. Baby boomers (those born 1945-1965) have the highest prevalence for HCV, correlating to a peak of infection in the mid-1980s that resulted from a contaminated blood supply prior to identification of the virus. Of the 6 genotypes of HCV, genotype (GT) 1 is the most common in the US.

The clinical and economic consequences of long-term infection are now emerging, with a growing proportion of HCV-infected individuals experiencing progression of fibrosis and cirrhosis, hepatocellular carcinoma (HCC), extrahepatic complications and death.

Estimating HCV Prevalence
How prevalent is CHC? In 2014, the Centers for Disease Control and Prevention (CDC) published a revised CHC prevalence estimate based on data from the 2003-2010 NHANES. Their findings indicate that CHC is present in 1.0% of the US population, or 2.7 million individuals (confidence interval [CI], 2.2-3.2 million).

This figure represents a possible decrease from the previous estimate, based on 1999-2002 NHANES data, of 1.3% of the US population, or 3.2 million individuals (CI, 2.7-3.9 million).

However, as the CDC researchers point out, because the CIs of these 2 estimates overlap, this decline may reflect the variability inherent in computing prevalence estimates from population samples. It might also relate to increased mortality among persons with HCV.

Estimates of CHC prevalence can differ widely based on the population sample surveyed. Prevalence estimates based on NHANES data are considered conservative because they are based on the non-institutionalized, civilian population—a cohort that does not include some groups known to have a higher rate of HCV infection, including homeless and incarcerated persons.

Using data derived from such sources as the US Census, the Centers for Medicare and Medicaid Services (CMS), the Bureau of Justice Statistics, and individual state departments of corrections, which include higher prevalence populations not assessed by NHANES, Chak and colleagues estimated CHC prevalence could range from 5.2 to 7.1 million individuals, or 2% of the total US population.
CHC Epidemiology and Disease Burden (cont.)

HCV-prevalent Populations

“Baby boomers”: CHC is most prevalent in persons born between 1945 and 1965—the so-called baby boomers. The CDC estimates that this birth cohort, despite comprising only 27% of the population, accounts for 75% of all persons with HCV in the US. NHANES data as of 2010 show an anti-HCV seroprevalence rate of 3.5% in baby boomers, which is more than 2.5 times the 1.3% seroprevalence rate in the general population.

Inmates: Prisoners represent approximately 29%-33% of the total US HCV cases. Their HCV prevalence of 12%-35% is 10->40 times higher than that of the general population (1% [CI, 0.8%-1.2%]).

Veterans: The estimated overall prevalence of HCV in veterans of 2.8% is over twice that of the general population. Based on data from 2011, the prevalence of HCV infection in the group of veterans that had undergone screening (2.9 million) was even higher at 6.2%.

Other groups: Anti-HCV seroprevalence is comparatively higher among men (1.9%) and non-Hispanic black persons (2.2%) versus the population as a whole.

Among participants in the 1999-2002 NHANES who were 40 to 49 years of age, 9.4% of non-Hispanic black persons were anti-HCV antibody positive compared with 3.8% of non-Hispanic white persons. Based on data from the 2003-2010 NHANES, the rate of current (ie, viremic) HCV infection in non-Hispanic black persons was nearly 4 times that in non-Hispanic white persons.

Prevalence of HCV Genotypes

There are 6 genotypes of HCV. GT 1 is the most common in the US, causing about 70%-78% of infections in the general population (Figure 1). GT 2 is the second most prevalent type of HCV at 13%-16% of infections, followed by GT 3 at 6%-12% of infections. Of individuals with GT 1 infection in the US, about 61%-66% have GT 1a and 34%-39% have GT 1b.

Genotype distribution can vary by subpopulation. GT 1 is present in an estimated 91% of non-Hispanic blacks and 70% of non-Hispanic whites with HCV infection. Among US veterans, 80% have GT 1 HCV infection, 11% have GT 2, and 7% have GT 3.

Figure 1. HCV Genotype Distribution in the US

CHC Epidemiology and Disease Burden (cont.)

HCV Infection Incidence

HCV incidence in the US peaked at an average of 230,000 new cases each year during the 1980s. Much of this was related to blood supply contamination before HCV was discovered in 1988. With the institution of universal blood supply screening in 1990-1992, the incidence of HCV declined >90%: from 2006 to 2010, based on reported cases, the CDC estimates 11,000 people each year became infected. However, based on reported cases in 2012 (the latest year for which data are available), the CDC estimates the incidence has increased 75% since 2010 to 21,870 cases. Although some of this increase may be attributed to more active surveillance by state and local health departments that received CDC funding for this purpose, the number of reported cases has increased outside of these locations as well. The CDC notes the trend also reflects an increase in acute HCV among adolescents and young adults, particularly in non-urban whites who have a history of opioid or injection drug use (IDU). Whether this increase represents a trend or an outlier is unknown.

HCV-related Liver Fibrosis and Cirrhosis

Chronic HCV causes ongoing, continuous liver damage over many years. Although progression of CHC-associated liver disease can be dynamic and difficult to predict, it has been estimated that by 30 years after becoming infected, >40% of persons will progress to cirrhosis. Given that HCV peaked in the 1980s, it follows that a large proportion of infected individuals have been living with CHC for 25–35 years. As the duration of CHC in the HCV-infected population has lengthened, data indicate cases of milder fibrosis have been declining, whereas cases of advanced liver disease have been increasing. The model constructed by Davis et al, which used conservative estimates of disease progression, projected ~30% of patients with CHC would develop cirrhosis by 2015 (Figure 2, p. 11). Razavi and colleagues, based on modeling of 1999-2002 NHANES data, project that the prevalence of severe fibrosis (F3) (ie, numerous septa without cirrhosis) and F4 (ie, cirrhosis) will surpass that of milder liver disease, and that the prevalence of compensated cirrhosis will reach 626,500 cases in 2015. A separate US population-based model using adjudicated claims data projected that advanced liver disease will increase from 195,000 in 2008 to 601,000 cases by 2015. At least 80% of these persons are projected to have cirrhosis (compensated or decompensated).

Following a similar upward trend, the prevalence of cirrhosis in a cohort of ~152,000 veterans with CHC increased from 5%-6% in 2005 to 13%-14% in 2009. In the key baby boomer demographic, modeling data from screening-eligible individuals (ie, those who did not already know their HCV infection status) estimated that in 2010, one-half had fibrosis grade F2 (portal fibrosis with rare septa) or above, and approximately one-third had F3/F4 liver disease.

CHC-associated Liver Disease Progression

Although sequelae from CHC generally take years to manifest, liver disease does not progress at the same pace in all patients. Duration of infection is consistently the most significant factor influencing progression. Certain cofactors and comorbidities, however, can increase the likelihood of more rapid disease progression (Table 1, p. 11).

• Co-infection: Multiple studies have established accelerated progression of HCV among human immunodeficiency virus (HIV)/HCV co-infected patients. This group has a higher prevalence of cirrhosis and fibrosis, with more rapid progression of fibrosis, and a greater incidence of hepatic decompensation than mono-infected patients. The relative risk for decompensation is sixfold higher in HIV co-infected versus mono-infected persons. Co-infection with hepatitis B virus (HBV) also can hasten disease progression.

• Diabetes: A retrospective analysis of outcomes in HCV-infected patients in the Veterans Administration (VA) clinical case registry system from 1999-2010 found that having diabetes significantly increased the risk of compensated and decompensated cirrhosis and HCC (P<0.001).

• Other factors: Other factors that elevate the risk of CHC-associated liver disease progression or more severe disease course include viral genotype, obesity, male gender, and older age at the time of infection. Persons who acquired HCV infection at age ≥30 years are 2- to 3-times more likely to progress to cirrhosis after 20 years than those infected at a younger age. Alcohol consumption (>50 g/d) and steatosis can also tip the balance toward faster progression of liver disease in persons with HCV.
depression, mixed cryoglobulinemia vasculitis, and lymphoproliferative malignancies (although the data showing an association between B-cell malignancies and CHC are inconsistent). 54, 55

Persons with HCV also have a high number of comorbid conditions. A retrospective cohort study using data from the Integrated Healthcare Information System (IHCIS) National Benchmark database from 1998 to 2006 (N = 7411 patients) found >99% of persons with HCV had ≥1 comorbid condition, 52% had 6-15 comorbidities, and 5.5% had ≥31 conditions. The rate of comorbidity in these individuals was nearly twice that in persons without HCV. 56
**Hepatocellular Carcinoma**

Hepatic decompensation and HCC can develop in persons with HCV. Presence of HCV infection, versus its absence, is associated with an approximately 25-fold increased risk for HCC. Individuals with viral hepatitis–associated cirrhosis have a higher incidence of HCC compared to those with non-viral cirrhosis. Data from a large private insurance database of patients with CHC in 2002-2010 found 15% had end stage liver disease (ESLD).

Based on a review of the literature, the absolute risk of developing HCC in patients with HCV-associated cirrhosis is estimated at about 3.5% annually. Another systematic review of 13 studies (N = 2386 patients) estimated that 3.4% of patients with compensated cirrhosis develop HCC each year, 6.4% progress to decompensation, and 4.6% undergo a liver transplant or die.

Data from Surveillance, Epidemiology and End Results (SEER) cancer registries show the US incidence of HCC increased 5.4% each year from 2000 to 2007 and 2.3% each year from 2007 to 2010. Currently, an estimated 50%-60% of persons with HCC in the US have HCV. Razavi et al projected that the prevalence of CHC-related HCC in the US will peak at 23,800 cases in 2018, and that of hepatic decompensation will peak at 107,400 cases a year later.

CHC prevalence data from other crucial populations also illustrate the impact of HCC:

- From 1996 to 2006, a 19-fold increase in HCC incidence was observed in US veterans, and by 2010, an estimated 2% of veterans with CHC in VHA care had been diagnosed with HCC.
- A study of men incarcerated in Texas from 2003-2006 showed they were 7 times more likely to have HCC, and 4 times more likely to die from it, than men in the general US population.

Although the overall increase in HCC incidence appears to be slowing, HCC mortality rates have increased significantly and steadily over the decade by 2.1% each year. In the age group with the highest prevalence of CHC, HCC incidence and mortality increased at much higher rates. From 2000-2006 and 2006-2010, HCC incidence in persons 50-64 years of age increased 9.6% and 5.2%, respectively, and mortality over the 10-year period increased 5.6% each year.

**Liver Transplantation**

HCV infection remains the most common diagnosis in adult liver transplant recipients. Between 1995 and 2010, 41% of 126,862 new primary US liver transplant registrants were infected with HCV. Between 2000 and 2010, the number of new liver transplant registrants with HCV and HCC in the baby boomer cohort (in this study defined as those born between 1941-1960) increased fourfold. In 2012, HCV infection accounted for the largest proportion of US liver transplant recipients, although the proportion (-25%) represented a decline from 2002 (32%). However, the second most common diagnosis for liver transplant recipients in 2012 was malignancy (22%), which increased almost threefold from 2002 (-8%). HCV infection likely contributed to the number of recipients with this diagnosis.

In a review of patients with HCC who received a liver transplant, Thuluvath and colleagues found that African Americans had a 21%-30% lower survival than others, after adjusting for other factors.

**HCV-associated Mortality**

The mortality rate from HCV is trending upward. A CDC analysis of death certificate data found a 50% increase in HCV mortality from 1999 to 2007. The ~15,100 deaths from HCV in 2007 outnumbered those from HIV that year. By 2010 (the latest year for which data are available), HCV mortality had increased an additional 9%-13% (~16,500-17,100 deaths) over the 2007 rate. Similarly, in their 2010 landmark study that used a dynamic, multicohort, natural history model to project CHC disease incidence and mortality, Davis and colleagues estimated 145,667 liver-related deaths due to HCV would occur in 2000-2009 (or ~14,550 each year). Their model projected increasing HCV mortality rates through 2022.

The annual number of deaths attributable to CHC likely is much higher. A recent comparison of mortality data between the Chronic Hepatitis Cohort Study (CHeCS) and the US multiple cause of death (MCOD) database in 2006-2010, suggests HCV is severely underrecorded on death certificates—even among persons who die from liver-related causes. HCV was listed on the death certificates of only 19% (n = 302) of the 1590 CHeCS participants with CHC who died during the study period, and it was included on only 29% (n = 46) of the certificates from 156 participants who had a liver transplant before death. Overall, the CHeCS liver disease mortality rate was 12 times higher, and the HCV mortality rate was 61 times higher, than the corresponding MCOD rates.

The mortality rate in persons with HCV is higher than in those without. Using the NHANES III Linked Mortality File, which includes data from adults whose HCV status...
CHC Epidemiology and Disease Burden (cont.)

HCV-associated Mortality (cont.)

was assessed in 1988-1994 and who were followed through 2006, El-Kamary and colleagues found all-cause and liver-related mortality rates that were more than 2 and 26 times higher in persons with CHC than without HCV infection, respectively. In this study, -58% of deaths from all causes and 96.2% of deaths from liver causes were attributable to HCV. Among persons with HCV in the US, annual mortality is expected to peak at -30,000 in 2019 for liver-related causes and -40,000 persons in 2022 for all causes.

Persons with HCV die at a younger age than those who are not infected. In a review of the top 10 causes of death derived from death certificates contained in the US MCOD data file for the year 2010 (N = 2.47 million), the median age of death was 55-59 years for persons with HCV. This was 12-32 years younger than the median age of death for persons not infected with HCV. It was also more than 20 years shorter than the average lifespan of persons living in the US. The CDC estimates that 73% of HCV-associated mortality currently occurs in baby boomers.

Economic Impact of CHC

Chronic HCV infection, along with its associated sequelae and complications, is costly to manage, and patients infected with HCV place a greater cost burden on the healthcare system than those who are not. Modeling data from Razavi et al, who used cost projections derived from an analysis of claims data from 50 million managed care enrollees in 2001-2010, estimated total HCV-associated direct medical costs in the US were $6.5 billion in 2011. Despite a projected decline in prevalence, costs are projected to continue increasing, and are expected to peak at $9.1 billion in 2024. Most of these costs will be related to advanced liver disease (compensated and decompensated cirrhosis and HCC), which is increasing as the population ages. Razavi’s model did not incorporate the impact of direct-acting antivirals (DAAs) or include any potential increase in HCV treatment or cure rates.

The cost of caring for individuals with HCV infection can increase dramatically with the severity of related liver disease. A recent study by Gordon et al of medical and pharmacy claims data from a private insurance database compared costs in patients (N = 53,796) with varying degrees of CHC-related liver disease severity, including non-cirrhotic liver disease (NCLD) and more advanced disease, for the years 2002-2010. The mean annual total healthcare costs for patients with cirrhosis were 1.3-times higher and for patients with ESLD were 3.5-times higher. Costs were 6.5-times higher than NCLD patients for those who developed HCC and 8.4-times higher for those who needed orthotopic liver transplantation (Figure 3). Overall, more than half of healthcare costs in this study (56%) were related to CHC, and this proportion also increased with severity of associated disease.

**Figure 3. Increasing Severity of HCV-related Liver Disease Associated with Increased Healthcare Costs**

Mean Annual All-cause Healthcare Costs for Cirrhosis and More Severe Liver Disease Relative to Non-cirrhotic Liver Disease (NCLD) Associated with HCV Infection

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Cost Ratio Relative to NCLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCLD (reference)</td>
<td>1</td>
</tr>
<tr>
<td>CLD</td>
<td>1.3</td>
</tr>
<tr>
<td>ESLD</td>
<td>3.5</td>
</tr>
<tr>
<td>HCC</td>
<td>6.5</td>
</tr>
<tr>
<td>OLT</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*Analysis of medical and pharmacy claims data, enrollment information, and linked laboratory results and mortality information from individuals enrolled for ≥1 year in US commercial health plans in a private insurance database. Data analyzed were from 2002 to 2010. Costs in 2010 US dollars. N = 53,796.

CLD = cirrhotic liver disease; ESLD = end-stage liver disease; HCC = hepatocellular carcinoma; OLT = orthotopic liver transplantation.

CHC Epidemiology and Disease Burden (cont.)

Economic Impact of CHC (cont.)

The higher cost of managing patients with CHC and associated liver disease reflects, in part, the higher rates of healthcare utilization in these patients compared with uninfected individuals. An analysis of data from the IHCIS National Benchmark database in 2000-2006 showed that a larger proportion of patients with CHC had been hospitalized (24%), visited the emergency department (ED) (32%), and had undergone lab testing (79%) compared with control patients without HCV (7%, 15%, and 35%, respectively; *P* < 0.0001 for all comparisons). At $6,864 per patient, disease-related costs were nearly one-third of all costs in patients with HCV. This exceeded all-cause costs among controls by 26%. 

Healthcare utilization also rises with increasing liver disease severity. Gordon et al. found that patients with cirrhosis and ESLD, respectively, had 1.18- and 1.55-times the number of ambulatory care visits than those with NCLD. Persons with HIV/HCV co-infection have more hospitalizations and ED visits than those with HIV mono-infection. This increased rate of healthcare utilization was not entirely because of liver disease but also was related to such comorbidities as diabetes, renal disease, and psychiatric conditions.

Screening for HCV

Before 2012, HCV screening was primarily reserved for those with risk factors. However, this approach proved suboptimal. The past 2 years have witnessed an increase in population-based screening in addition to risk-based screening. Currently, the CDC and United States Preventive Services Task Force (USPSTF) recommend 1-time HCV screening for all baby boomers, regardless of their risk factors. This generally has been shown to be cost-effective and is expected to reduce morbidity and mortality from CHC. Professional societies and the World Health Organization (WHO) have joined the CDC in recommending population-based screening to proactively identify persons who will need further evaluation for HCV. Such broad-based screening will require enhanced awareness by both patients and healthcare professionals in order to gain traction.

Risk-based Screening

IDU remains the number 1 risk factor for acquiring new HCV infection. A meta-analysis of 4 US national surveys (the National Survey of Family Growth, National Survey of Drug Use and Health, NHANES, and the General Social Survey) conducted from 1999 to 2009 estimated the prevalence rate of HCV infection in IDUs aged 40 to 65 years was 43,126 per 100,000 persons in 2011. Those who are more likely to be exposed to HCV-contaminated blood, including healthcare workers, individuals with hemophilia, and persons who receive tattoos with improperly sanitized needles (especially in corrections settings) are also at an increased risk of infection. Receiving either a blood transfusion or a solid organ transplant before July 1992 or hemophilia clotting factors manufactured before 1987 are other HCV risk factors.

Before 2012, the CDC recommended routine HCV testing only for persons with specific risk factors. This met with limited success, however, as evidenced by the substantial number of persons who were unaware they had HCV. A follow-up survey of participants in the 2001-2008 NHANES found that about 50% of HCV-positive individuals did not know they were infected. Of those who did know, only 3.7% said they had first been tested (before participating in NHANES) because they or their physician thought they were at increased risk; about 46% were tested because they had routine blood work that indicated potential liver disease.

Even in high-risk groups for whom the CDC recommended testing, the rate of HCV screening varies widely in the literature from 17% to 87%. Studies have found suboptimal HCV screening rates even among patients with ≥2 tests showing abnormal alanine aminotransferase (ALT) levels or such risk factors as known injection drug use and HIV or HBV co-infection. Data from the Kaiser Permanente mid-Atlantic states database from January 2003 to December 2012 (n = 444,594) showed that individuals born in the years 1965-1994 (screening rate = 19%) were more likely to be screened for HCV than baby boomers (persons born in 1945-1964; screening rate = 14%). Also, females were more likely to be screened than males, who comprise a larger proportion of the HCV-infected population. Risk-based HCV screening is further complicated because many HCV-infected persons do not recall or report having any specific risk factors.
Screening for HCV (cont.)

Rationale for Birth Cohort–based Screening

Over the past 2 years, there has been a major change in the focus of HCV screening recommendations. US public health authorities are shifting away from relying solely on risk factor-based screening to incorporate population-based screening for the baby boomer birth cohort. The CDC in 2012 and the USPSTF in 2013 had added a recommendation that everyone born from 1945 to 1965, regardless of risk factors, receive 1-time screening for HCV. Against the background of limited efficacy of risk-based screening for HCV, the increasing morbidity and mortality from CHC-associated disease, and advances in anti-HCV therapy, both authorities cite the disproportionately high prevalence of HCV in this birth cohort as rationale for their recommendation. The CDC and the USPSTF also continue to recommend screening for groups traditionally at high risk for HCV. Population-based HCV screening in baby boomers helps to detect the substantial number of cases that are missed because individuals are either unaware of or do not report their risk status.

Screening Recommendations from Other Organizations

Guidelines from other health authorities generally recommend HCV screening for groups and populations with either HCV risk factors or a known higher prevalence of infection.

Professional societies: Similar to the guidelines from the CDC and USPSTF, the 2014 updated guidance for testing, managing, and treating HCV from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend 1-time HCV screening for baby boomers in addition to risk-based screening. WHO: Updated guidelines from the WHO advise testing for individuals with HCV risk factors similar to those mentioned in the CDC and USPSTF recommendations. Because of differences in geographical settings and populations, the WHO does not specifically mention baby boomer testing but does recommend “testing be offered to individuals who are part of a population with high HCV seroprevalence.”

US Department of Veterans Affairs: The VA recommends HCV antibody testing for individuals with traditional risk factors (eg, past or current IDU, HIV positive, transfusion/organ transplant before July 1992) as well as for all Vietnam veterans (people who served between 1964 and 1975) due to the high prevalence of HCV infection in this population.

Federal Bureau of Prisons (FBOP): These guidelines contain no recommendations for population- or birth cohort-based screening. Instead, they recommend HCV antibody testing for inmates on chronic hemodialysis, with elevated ALT of unknown etiology, and with extrahepatic HCV manifestations (mixed cryoglobulinemia, membranoproliferative glomerulonephritis, or porphyria cutanea tarda) regardless of sentencing status as well as sentenced inmates who have other traditional risk factors for infection, including specifically recommending HCV screening for individuals who received tattoos or piercings while incarcerated.

Health Economic (HECON) Considerations of Birth Cohort–based Screening

Based on modeling data, birth cohort screening generally has been shown to be cost-effective and is expected to reduce morbidity and mortality from CHC. Furthermore, in analyses that compared different screening approaches, birth cohort screening provided more benefit per dollar spent when compared with risk-based screening, although the cost per quality-adjusted life year (QALY) gained was sensitive to several factors, including the risk of disease progression within a population; the percentage of the population that was screened; the cost of anti-HCV therapies; and the rates of referral, treatment, and cure.

Policy Implications of Screening Recommendations

The USPSTF HCV screening recommendations, which include the recommendation for 1-time testing of baby boomers, were given a Grade B recommendation. The Affordable Care Act (ACA) contains a provision that requires non-grandfathered group health plans and health insurance issuers offering group or individual health insurance coverage to provide coverage for in-network preventive care services without any cost-sharing (co-payments, coinsurance, or deductible). Among the preventive services that must be covered with no cost-share are those given A and B recommendations by the USPSTF. In light of this, the CMS announced in June 2014 that it will cover screening for HCV when ordered by a patient’s primary care provider. This applies to adults at high risk for infection as well as 1-time screening for those born from 1945 to 1965 who are not otherwise considered high risk.
Screening for HCV (cont.)

Policy Implications of Screening Recommendations (cont.)

New York State passed a law, effective January 1, 2014, that mandates HCV screening be offered to all baby boomers (i.e., those born between 1945 and 1965) receiving healthcare services as an inpatient of a hospital or an outpatient in a hospital or primary care clinic/practitioner’s office. The law does not require providers to perform HCV testing but does stipulate that practitioners must proactively offer it rather than simply saying it is “available.” With such policies emerging only within the past year, whether any of these policies will increase HCV screening rates has yet to be determined.

Screening Tests and Protocols

In 2013, CDC issued an updated guidance for clinicians and laboratorians concerning the HCV testing protocol: the initial screening for HCV antibody can be lab-based via enzyme immunoassays (EIAs) or done at the point-of-care via rapid antibody testing. (Recombinant immunoblot assay [RIBA], a supplemental HCV antibody test previously recommended by the CDC, is no longer available.)

A reactive EIA should be followed up with nucleic acid testing (NAT) testing, which remains the gold standard for HCV RNA detection and diagnosis of active HCV infection. A reactive result on a point-of-care assay then also requires venipuncture and lab work-up for confirmation of ongoing HCV infection using NAT.

Individuals with both a reactive antibody test and a positive HCV RNA test are potential candidates for treatment; those with a reactive antibody test and a negative HCV RNA test do not have chronic HCV infection and, in most cases, require no further follow-up.

In its 2013 revised HCV screening guidance, the USPSTF cited the accuracy of tests used to detect CHC infection—specifically, HCV antibody testing followed by NAT via qualitative polymerase chain reaction (PCR) assay to confirm viremia—as an important factor influencing its revised screening recommendations.

There are currently no data available concerning the proportion of HCV screening done via lab-based EIA versus rapid antibody testing.

HCV Screening Trends

Data are limited regarding rates of HCV screening but generally illustrate persisting barriers. A study of eligible baby boomers visiting a Washington, DC primary care clinic between December 2012 and February 2014 (N = 5497), found that 26% of these individuals were not tested for HCV, even though their physicians had been notified via electronic medical records that they should be tested. A recent online survey of US ED physicians (n = 67) and mid-level healthcare providers (n = 11) found that 42% were unaware of the 2012 CDC guidelines for HCV screening in baby boomers. In a review of the literature to identify gaps in HCV diagnosis and management, Yehia and colleagues found that out of 3.5 million people estimated to have CHC, 50% were diagnosed and aware of their HCV status, 43% had access to outpatient care, and only 27% had HCV RNA confirmed.

Knowledge among the general public concerning HCV infection also remains low. In an anonymous, prospective survey of a sample of New York City ED patients and pharmacy clients in 2010-2011 (N = 2078), less than half knew what HCV was. Individuals who were older or who knew of the virus were significantly less likely to accept being tested, highlighting the importance of patient willingness in increasing screening rates.

Screening in alternative locations could be important for increasing the number of persons who are tested. In 2011-2012, a subset of participants (n = 4689) in the CDC’s Chronic Hepatitis C Cohort Study (CHeCS) were asked where their initial HCV test had occurred in 2006-2010. Although about 60% initially had been tested in a physician’s office, nearly 33% of tests had been conducted in alternate settings. Nearly half of those surveyed only sought testing after experiencing clinical indications of liver disease.

The potential importance of increasing HCV screening rates is underscored by data from an analysis of mortality (2000-2011) in New York City residents diagnosed with HCV. More than half of these persons died within 3 years of their infection status being reported to the New York City Department of Health and Mental Hygiene, indicating they may not have undergone testing until symptoms emerged. However, there are no data in the literature concerning the impact of HCV screening (versus no screening) on clinical outcomes or the comparative clinical effects of alternative screening strategies.
Diagnosis of HCV-associated Liver Disease

HCV treatment is a process that starts with screening and proceeds to anticipated successful outcomes. However, gaps exist along the pathway to cure. Currently, a substantial percentage of persons living with HCV in the US are not referred for treatment. Linkage to care is especially low for underserved or marginalized populations and those without health insurance. Emergence of noninvasive diagnostic tools and recommendations for their use within guidelines/guidance may further simplify the diagnostic approach to HCV.

From Screening to Diagnosis: Linkage to Care

Gaps from screening to professional care: Screening for HCV informs individuals of their infection status, but is only the first step on the pathway to treatment and cure. Linkage to care represents the crucial next step for further evaluation, diagnosis of liver disease, and treatment—one that often is not taken:

- Based on NHANES HCV prevalence estimates and data on diagnosis and treatment from CHeCS, only an estimated 34% of persons living with HCV infection in the US are referred for care.

- Among a sample of HCV-positive racial and ethnic minority participants (N = 859) in the 2009-2010 Racial and Ethnic Approaches to Community Health Across the US Risk Factor Survey, only 44% reported they were currently seeing a physician for HCV infection. Patients who were >35 years of age, diagnosed >2 years, or without health insurance were less likely to be on treatment.

- Linkage to care can be particularly problematic for underserved or marginalized populations and for those such as the homeless, mentally ill, and corrections populations, who may mistrust or exist outside of the formal healthcare system. In 2009, the Massachusetts Department of Public Health Bureau of Infectious Disease began an HCV screening and education pilot project at the Barnstable County Sheriff's Department in Massachusetts called The Screening for Hepatitis C as a Prevention Enhancement (SHAPE) initiative, which was integrated into already existing HIV services. In 2009-2011, SHAPE provided inmates (N = 2716) with hepatitis and liver health education and opt-in HCV antibody testing (n = 596 accepted testing) at intake, and referral to community clinicians upon release. Only 38% of inmates who tested HCV positive while incarcerated (n = 122) received medical care for the infection after their release.

Gaps in referral to specialists: There is also evidence of a gap in the linkage to care for HCV-positive patients with respect to referrals for specialist evaluation:

- An analysis of follow-up interviews conducted in NHANES 2001-2010 participants who screened positive for HCV (n = 205) showed that, although 81% had sought the care of a doctor after learning of their HCV status, only 52% had regular follow-up recommended.

- A retrospective analysis of patient visit, patient referral, HCV RNA testing, and treatment initiation data from 458 patients who screened anti-HCV positive in primary care at an integrated health system in 2005-2010 found only ~60% were referred to a specialist (Figure 4, p. 18).

- A recent survey of 188 IDUs participating in a syringe exchange program found that 62% of those who were HCV positive had never seen an HCV specialist, even though only 36% were uninsured.

Diagnostic Tests

Biopsy: For over half a century, liver biopsy has been considered the gold standard for assessing HCV-related liver damage, including identifying, grading, and staging the extent of fibrosis. Biopsy is also advantageous for evaluating abnormal liver function tests (LFTs), differentiating fibrosis from cirrhosis, clarifying diagnostic uncertainty, and evaluating the extent of necroinflammation in liver tissue. Although biopsy can provide the most complete set of information about the extent of liver disease, it does have limitations. Chief among these is that it is an invasive procedure associated with a low but real risk for complications, including hypotension, bleeding, and perforation. Patients commonly find liver biopsy to be painful and may be reluctant to undergo the initial or repeated procedures because of pain concerns. In addition, the accuracy of liver biopsy can be compromised by inadequate tissue sampling, sampling error, and misinterpretation of liver histology. Up to one-third of bilobar biopsies can have a difference of ≥1 fibrosis stage between the lobes. The procedure can also be costly, and regular, repeat biopsies are needed to monitor disease progression.
Diagnosis of HCV-associated Liver Disease (cont.)

Diagnostic Tests (cont.)

Noninvasive methods: During liver-directed physical examination, the physician palpates the liver to assess firmness. Results are normal in most patients.\textsuperscript{13} Other noninvasive methods for assessing HCV-associated liver disease include direct markers, which assess extracellular matrix metabolism, and indirect markers, which include serum markers of hepatic function as well as imaging techniques that assess liver stiffness via transient ultrasound elastography, acoustic radiation force impulse, or magnetic resonance elastography. In general, these noninvasive procedures are most useful for differentiating severe from mild fibrosis, but are less useful for determining specific grades of fibrosis.\textsuperscript{13,111} No single noninvasive test is recognized to have high accuracy for diagnosing degree of fibrosis when used alone.\textsuperscript{13}

Transient elastography, or FibroScan\textsuperscript{*}, which was approved by the FDA in 2013 to aid in the clinical management of patients with liver disease,\textsuperscript{113} can provide instant information regarding liver stiffness at the point-of-care.\textsuperscript{13} This is an important advantage over biopsy. Health plans are increasingly accepting this technology for evaluation of liver disease, and its use was recently facilitated by the assignment of a specific reimbursement code.\textsuperscript{114} However, the FibroScan\textsuperscript{*} machine is expensive to purchase. Furthermore, it can only reliably distinguish the presence or absence of cirrhosis.\textsuperscript{13,111} Studies have also found that certain factors, including higher body mass index (BMI), patient age and gender, presence of type 2 diabetes mellitus and hypertension, eating a meal within 120 minutes of scanning, CHC-associated inflammation, extrahepatic cholestasis, congestive heart failure, and amyloidosis may influence the scan’s interpretability and/or reliability.\textsuperscript{115-118}

The latest AASLD/IDSA guidance recommends combining direct biomarkers with transient elastography for initial assessment of liver fibrosis severity. Should there be any discrepancies between these 2 tests, biopsy can be considered if the results would affect clinical decisions. This approach is the most efficient diagnostic method and reduces the need for biopsy. If clinicians do not have access to transient elastography or direct biomarker testing, the guidance recommends the aspartate aminotransferase-to-platelet ratio index (APRI) or fibrosis-4 index (FIB-4), which can help distinguish F3/F4 fibrosis from less severe disease. In this case, biopsy should be considered if more accurate fibrosis staging is needed. Finally, patients with clinically evident cirrhosis require no additional invasive or noninvasive testing.\textsuperscript{13} There are no published studies at the time of this report that have investigated the proportion of HCV-infected patients who undergo noninvasive fibrosis measurements in lieu of biopsy.
Treatment Considerations

The goal of treatment is SVR, which is considered virologic cure. Patients who achieve SVR may have reduced HCV-related downstream costs on the healthcare system. The rapid evolution of the HCV landscape in recent years has compelled both government and professional entities to likewise evolve their approach to revising HCV management guidance, in some cases eschewing formal publication in order to rapidly disseminate information to healthcare providers.

Defining Treatment Goals

The goal of therapy for HCV infection is SVR, defined as the lack of detection of HCV RNA in the blood a few months after a patient completes a course of antiviral therapy. SVR is considered virologic cure.15 Previously, SVR was measured at 24 weeks after patients completed treatment. However, the FDA now accepts SVR at 12 weeks post-treatment completion as an appropriate primary endpoint for registrational trials and regulatory approval of CHC therapies.15 Unlike other viruses associated with chronic infection—such as HBV or HIV, which can maintain a latent viral reservoir—HCV is a non-integrating RNA virus. Therefore, recurrence of HCV infection in patients who achieve SVR with antiviral treatment is very rare (<1%).119-120

Impact of Achieving SVR

Numerous studies support the long-term improvement in CHC outcomes, including liver-related and all-cause mortality, in patients who achieve SVR.17,121,122 In the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial, a prospective, multicenter study of patients with advanced CHC-associated fibrosis (N = 449) followed for 7.5 years, rates of liver-related and all-cause mortality, decompensated cirrhosis, and liver transplants were significantly reduced in patients who achieved SVR versus those who did not (P≤0.012). Patients who achieved SVR also experienced fewer cases of any liver-related outcome, including ascites, variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis.121 Achieving SVR has been shown to reduce all-cause mortality by approximately fourfold relative to not achieving SVR.16 Achieving SVR even reduces all-cause mortality in populations, such as US veterans,122 having higher background rates of comorbid conditions and in patients with HCV/HIV co-infection.123 Although SVR greatly reduces the risk of patients developing HCC, it does not completely eliminate it.18,121 Persons who have advanced liver disease will require long-term follow-up and HCC surveillance regardless of whether or not their treatment results in SVR.13

HCV Treatment Guidelines

CHC infection continues to be managed with combination treatment regimens. These may include pegylated interferon (Peg-IFN), which induces the innate antiviral immune response;124 ribavirin (RBV), which inhibits RNA replication (although the exact mechanisms are not well understood);125 and DAAs, which directly interact with and inhibit certain viral proteins involved in the HCV lifecycle.124,126 Choice of treatment regimen varies by genotype.13

In an unprecedented collaboration, AASLD, IDSA, and the International Antiviral Society of the United States of America (IAS-USA), jointly released recommendations in 2014 for testing, managing, and treating HCV.13 For physicians and payers alike, this partnership is important because it emphasizes the concordance between hepatologists and infectious disease experts about evidence-based HCV management protocols. Citing the substantial evolution in the HCV treatment landscape since 2011 (the year the previous AASLD guideline update was published15) and the expected rapid increase in the “pace of change,” AASLD and IDSA “developed a Web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations” (www.hcvguidelines.org) in preference to publishing the guidance in a medical journal.13 AASLD and IDSA promise rapid and frequent updates to recommendations as new data and treatments become available. Other organizations, including WHO, the European Association for the Study of the Liver (EASL), the VA, and the FBOP, also released updated recommendations in the first 6 months of 2014, another indication of the rapid pace of change and the importance health authorities are placing on incorporating new data on testing, managing, and treating HCV into their guidelines.84,86,128,129

Pretreatment, On-treatment, and Post-treatment Testing

Prior to treatment initiation, AASLD/IDSA recommends quantitative HCV RNA testing, to determine baseline level of viremia, and testing for HCV genotype, to guide selection of antiviral regimen. Pretreatment assessment of hepatic fibrosis is recommended via noninvasive testing or biopsy in order to guide the decision to treat. In addition, the guidance recommends any additional pretreatment tests required for specific therapies, such as baseline mutation testing; pregnancy testing; routine blood tests, such as serum ALT, albumin, bilirubin, international normalized ratio level, and complete blood count (CBC) with platelets; and liver and renal function testing.13
Treatment Considerations (cont.)

Pretreatment, On-treatment, and Post-treatment Testing (cont.)

The 2014 US FBOP treatment guidance notes that although there are several ways to determine the degree of fibrosis before starting anti-HCV treatment, liver biopsy is no longer required unless otherwise clinically indicated. To determine the presence of advanced fibrosis/cirrhosis in inmates, the guidance recommends APRI but also notes that such imaging studies as ultrasound and computed tomography scanning may identify findings consistent with cirrhosis.\(^{129}\)

A 2011 study using a Markov model to compare the cost-effectiveness of anti-HCV treatment, with or without preliminary liver fibrosis diagnostic testing (liver biopsy or FibroSURE\(^{\text{TM}}\)) found that even factoring in the cost of protease inhibitor (PI) therapy for GT 1 HCV patients, incremental cost-effectiveness ratios (ICERs) for treating without testing were below the $50,000 per QALY threshold. Therefore, the model showed that it was cost-effective to treat all patients with HCV without initial fibrosis staging.\(^{130}\) No data are available to provide an estimate of the proportion of patients who undergo liver biopsy before treatment.\(^{12}\)

The need for on-treatment monitoring varies based on label recommendations and underlying risks of different antiviral agents used in treatment. The AASLD/IDSA guidance recommends ongoing assessment of liver disease for patients in whom treatment is deferred, in patients who failed to achieve SVR, and in patients with more advanced fibrosis who achieve an SVR with treatment.\(^{13}\) There are no data available concerning how often any of these or other types of tests are used before or during antiviral treatment of patients with CHC.

HCV Treaters

Evidence from the literature indicates treatment of HCV in the US remains primarily the responsibility of liver, gastrointestinal, and infectious disease specialists. For example, in a 2005-2009 survey of veterans (N = 151,965) being treated for HCV (including those living in rural or highly rural areas with considerably less access to specialty care), only 23%-27% were receiving therapy from a provider who was not a hepatologist, gastroenterologist, or infectious disease specialist.\(^{46}\) Access to specialist care remains an important barrier to treatment of HCV.\(^{13}\) Gaps in the literature exist about which healthcare providers (eg, hepatologists vs infectious disease specialists vs primary care clinicians) are treating CHC, the proportion of practices devoted to CHC patients, and the time it takes to manage a patient with HCV.

Who is Being Treated

Selection of patients for treatment is a matter of intense discussion as providers and patients weigh the “treat or wait” decision. Although the number of patients being treated is beginning to increase, a significant number of patients are being deferred for both clinical and non-clinical reasons.\(^{131}\)

Clinical factors that influence the treatment decision include infection genotype and severity of CHC-associated disease.\(^{132,133}\) A cross-sectional study involving online survey and interviews of a convenience sample of individuals in the US with known HCV infection (treatment naïve and experienced; N = 138) found key barriers to beginning treatment included being asymptomatic, difficulty of the regimen, fear of side effects, and lack of health insurance. Patients planning to begin therapy cited having symptoms and receiving doctor recommendations among key motivators.\(^{134}\) Physicians are more likely to initiate—and patients more likely to accept—therapy in cases of more severe liver disease.\(^{135}\)

Given the anticipated increasing prevalence of moderate-to-severe fibrosis and decreasing prevalence of mild fibrosis,\(^{8,47}\) the majority of patients being treated today are likely to be those with more advanced liver disease. Although few data are available concerning the fibrosis severity in patients being treated today, a syndicated patient chart audit conducted by Ipsos in the first quarter of 2014 indicated that <40% of treated patients with CHC had minimal to no liver damage.\(^{131}\)

Trends in CHC Treatment

Although estimates vary, the percentage of persons with HCV who are treated remains low. The treatment capacity of US treaters and the volume of patients likely to be treated remain a challenge to estimate, and results of an analysis of the treatment cascade show significant gaps all along the path to HCV cure. Treatment can be delayed for any number of clinical and nonclinical reasons.
Trends in CHC Treatment (cont.)

Who is Being Treated (cont.)

In August 2014, the AASLD/IDSA issued guidance concerning when and in whom to initiate HCV antiviral therapy.13 This guidance recommends treatment for all patients with chronic HCV infection with the goal of achieving SVR early in the course of infection before severe disease and other complications can develop. However, the guidance acknowledges resource and capacity limitations may complicate treating all patients with CHC in a short amount of time. Where these limitations exist, patients with advanced fibrosis (F3), compensated cirrhosis (F4), severe extrahepatic HCV, and those who have received liver transplants should be assigned the highest priority. The most immediate and high-impact benefits of treatment may be realized in these patients. The guidance also notes that “Based on available resources, treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority.” These include patients with F2 fibrosis, HIV or HBV co-infection, other coexistent liver disease (such as non-alcoholic steatohepatitis), debilitating fatigue, type 2 diabetes mellitus, or porphyria cutanea tarda. The guidance further emphasizes that successful treatment of those at an increased risk of transmitting HCV to others may result in long-term benefits (e.g., decreased transmission and reinfection rates).13

HCV Treatment Rates

Although estimates vary based on population, the percentage of individuals with HCV who are treated for the infection overall is low. Yehia and colleagues,4 in their review of the literature, found that only 16% of people with CHC in the US have been prescribed treatment and 9% achieved SVR (Figure 5). The 2005-2010 analysis of data from an integrated health system found that only about 6% of patients with HCV received treatment.109 A retrospective database study of commercial and managed Medicare insurance claims from 2009 to 2012 (N = 3732) by Brooks et al135 found the treatment initiation rate for HCV was 8%-12%.

Historical Treatment Trends

Peak HCV treatment rates in the US occurred in 2003, at approximately 140,000 individuals.136 The introduction of Peg-IFN in 2002 and PIs in 2011 resulted in a modest gain in the number of CHC patients receiving treatment. However, this increase was short-lived.136-138 Results of a study conducted by Chen and colleagues139 at 2 hepatology practices in Dallas and Miami in 2011-2012, the first year after FDA approval of the PIs boceprevir and telaprevir, illustrates this trend. This study found that although there was an increase in patient visits to the practices in the months immediately following the approval of the DAAs, only about 19% of patients (N = 487) with HCV GT 1 had received DAA-based therapy, which was nearly the same as the reported proportion of patients treated with Peg-IFN and RBV prior to the approval of the DAAs. Similarly the analysis of insurance claims data by Brooks and colleagues135 found that the introduction of PIs did not substantially change treatment rates (8%-12% prior to their introduction vs 9%-10% afterwards).

![Figure 5. Estimated Rates of HCV Diagnosis, Treatment, and SVR in the US](image-url)
Trends in CHC Treatment (cont.)

Future Treatment Trends

Over the next 3 years, the introduction of the new therapies is projected to steadily increase HCV treatment rates within the commercially insured population, the numbers of which will then begin to decline (Figure 6).\textsuperscript{14} According to a 2014 Health Research Institute (HRI) forecast based on estimates from Truven Health Analytics claims data from employers and NHANES, assuming there are about 3.3 million persons with HCV in the US, about 60,000 commercially insured patients with HCV will be treated in 2014. This number is projected to rise to just over 80,000 by 2016 and then decline gradually each year thereafter. The analysis assumes about 30% of treated patients have commercial insurance.\textsuperscript{14}

More recently, an individual-level state-transition model was developed to simulate the HCV infected population from 2001-2050 and study the impact of new therapies and screening on chronic HCV infection and associated disease outcomes. Even in an ideal scenario involving perfect 1-time cohort screening, adoption of new therapies as they become available, and unlimited treatment capacity, this model estimated it would take 12 years for HCV to become a “rare disease” (affecting 1 in 1500 persons or less). Under a base case that more closely resembled current clinical practice, the model estimated that it would take until 2036 for HCV to become a rare disease.\textsuperscript{140}

Considerations for Health Economics of HCV Treatment

The cost of treating CHC encompasses expenditures beyond the cost of medications and can include adverse event and drug management costs, monitoring costs (eg, lab tests, office visits), and health state costs (eg, office visits, hospitalizations).

Anti-HCV treatment helps mitigate the cost burden of HCV infection. In a follow-on analysis of the 2002-2010 study using medical and pharmacy claims data from a private insurance database (N = 33,309), Gordon et al\textsuperscript{20} showed that anti-HCV treatment was associated with follow-up healthcare cost reductions. HCV-related total costs and total healthcare costs were 33%-58% and 22%-35% lower, respectively, in treated vs untreated patients. These findings were independent of baseline patient comorbidities and stage of CHC-associated disease. This analysis, however, did not include the costs of PIs, and treatment was limited to IFN, Peg-IFN, and RBV only.\textsuperscript{141} A separate analysis of US medical and pharmacy claims data from 2002-2006 found that patients who were adherent to anti-HCV therapy (Peg-IFN and RBV) had higher pharmacy costs but significantly lower total HCV-related costs when pharmacy was excluded.\textsuperscript{141}

Figure 6. Projected Number of Privately Insured HCV Patients Treated with Prescription Drugs over the Next Decade\textsuperscript{14*}

*PwC Health Research Institute estimate based on National Health and Nutrition Examination Survey and 2012 Truven Health Analytics claims data from employers. Forecast is based on a population of about 3.3 million patients with HCV, an estimated 60,000 patients who receive treatment per year, and an estimated 16,000 new cases discovered each year. This analysis assumed that about 30% of treated patients have commercial insurance.

Considerations for Health Economics of HCV Treatment (cont.)

In the past 2 years, the results of multiple cost-effectiveness Markov models based on US clinical trial and hypothetical populations have been published concerning Peg-IFN + RBV therapy, triple therapy, and other DAA therapy regimens in various patient groups, including treatment-naïve, treatment-experienced, and treatment-ineeligible patients; patients infected with different HCV genotypes; and veterans.\textsuperscript{142-148} Cost-effectiveness models for HCV treatment, as for treatment of any disease, seek to estimate the value of investment in an intervention and provide decision makers with information to assist in allocating limited healthcare resources.\textsuperscript{149} To do so, they weigh assumptions about the natural history of CHC-associated disease, the likelihood of disease progression, and the costs of managing sequelae against the cost of treatment, the likelihood of SVR with treatment, and any offset in disease management costs anticipated by curing HCV infection.\textsuperscript{142,148}

In addition to the cost-effectiveness models published in the literature, several outside reports, including those from Milliman,\textsuperscript{22,23} the California Technology Assessment Forum and Institute for Clinical Economic Review,\textsuperscript{24} the California Healthcare Institute,\textsuperscript{25} and Oregon Health & Science University\textsuperscript{26} have been produced in the past 2 years. These reports provide analyses of the value or cost impact of specific new therapies, the validity of new treatment recommendations, and the potential effect of new screening recommendations and increased treatment rates on the HCV landscape in general or for specific market segments. Produced by a variety of stakeholders, these reports present conflicting findings and viewpoints on the impact of current trends in the HCV marketplace. Echoing the data gaps, a driver of this variability is the underlying rate of patient diagnosis and treatment.

The cost of treating CHC encompasses expenditures that should be considered beyond the cost of therapy. Additional treatment cost components may include adverse event and drug management costs, monitoring costs (eg, lab tests, office visits), and health state costs (eg, office visits, hospitalizations).\textsuperscript{142,148,150-152} Considering treatment costs in the context of SVR rate provides a more holistic view of the total costs associated with curing HCV.\textsuperscript{150,152,153} Cost-effectiveness analyses and cost/SVR calculations for antiviral therapy appear to have increasingly more influence on HCV management decisions. As noted in the AASLD/IDSA guidance, "the choice of treatment may, in the future, be further guided by data from cost-effectiveness studies."\textsuperscript{113}

Considerations for Specialty Pharmacy

As HCV treatment rates increase and new therapies become available, the role of specialty pharmacies in dispensing these medications and supporting their management may also increase.\textsuperscript{154} Specialty pharmacies can help track HCV antiviral therapy usage to ensure patients are receiving and taking the medications as prescribed.\textsuperscript{155} Specialty pharmacy services also include patient counseling and training about administering medication, identifying and managing medication side effects, coordinating with prescribers, and assisting with administrative issues (eg, prior authorizations).\textsuperscript{154,155}

These services can facilitate HCV treatment by helping boost patient adherence to antivirals, which optimizes the potential for SVR and may reduce total HCV-related costs.\textsuperscript{141,154} An analysis of HCV medication claims from a large, national pharmacy benefit management company database (N = 2230) from 2007 to 2009 found patients who received their HCV antiviral medications exclusively from a specialty pharmacy had a ~9% higher adherence rate compared with those who received their medications from a retail pharmacy. Also, a higher proportion of specialty pharmacy patients had ≥80% regimen adherence versus retail pharmacy patients.\textsuperscript{154}

Trends in Special Settings

Veterans

Veterans are a population with an increased CHC burden.\textsuperscript{2-35} They also are considered to be highly screened: as of 2011, before updates to the CDC/USPSTF screening recommendations, an estimated 53% of all veterans (2.9 million) and 64% of those born between 1945 and 1965 had been screened for HCV by the VA. The rate of confirmatory HCV RNA testing was ~95%. In the screened cohort, the prevalence of ongoing HCV infection was 6.2% overall and 10.3% in baby boomers.\textsuperscript{36} In 2010, an estimated 14% of the >165,000 veterans with CHC in VA care had cirrhosis. Common comorbidities included hypertension, depression, and type 2 diabetes mellitus.\textsuperscript{35}
Trends in Special Settings (cont.)

Veterans (cont.)

Perhaps as a reflection of the high screening rate, data indicate that veterans have higher HCV treatment rates than the general population. Two studies identifying veterans with CHC using the VA HCV Clinical Case Registry from 2000 to 2005 and from 1999 to 2010 estimated the HCV treatment rates at 12% and 24%, respectively. However, these studies also estimated that only 3.5%-4% of all veterans with CHC achieved SVR, which is less than the estimated 9% of successfully treated HCV-positive individuals in the US population as a whole. In veterans treated from 1999 to 2010 who achieved SVR, the risks of liver-related clinical events (newly diagnosed cirrhosis [compensated or decompensated], HCC, or liver-related hospitalization) and mortality were reduced by 27% and 45%, respectively, compared with those who remained HCV positive. Updated 2014 treatment recommendations from the VA note that all veterans with HCV who are suitable for treatment and who wish to be treated should expect to be treated. Treatment is considered urgent for patients with “advanced cirrhosis, selected patients with HCC awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extrahepatic manifestations of HCV.” For patients with milder (F0-F2) liver disease, delaying treatment may be considered in light of anticipated new therapies on the horizon.

Corrections

HCV prevalence is estimated to be substantially higher in persons who are incarcerated versus those who are not. Data from surveillance studies in this population, however, are sparse. The CDC estimates the prevalence of CHC in prison inmates to be 12% to 35%. Other studies report similar results:

- A meta-analysis of data from 14 published and unpublished sources collected through September 2012 estimated a 29% HCV antibody seroprevalence in the corrections population in all of North America.
- A survey of states performing HCV screening in inmates from 2001 to 2012 (n = 12) estimated that >1.8 million individuals with HCV, or 28.5%-32.8% of all US cases (based on 2006 NHANES estimates) were incarcerated. The data yielded a seroprevalence estimate of 17.4% of the 2006 national state prisoner population.

- Screening of IDUs newly incarcerated at 2 Massachusetts correctional facilities in 2006-2008 estimated an acute HCV seroprevalence rate of 20.5% (N = 3470).
- Based on limited published data, the prevalence of HCV in inmates with HIV-1 is estimated to be 38%-70%.

Receiving a tattoo in prison is considered a risk factor for HCV infection, indicating concern over transmission between incarcerated individuals. A meta-analysis of incidence rates in corrections settings indicates intraprison incidence of HCV is higher than the incidence in the US population, but lower than that among recidivist detainees and IDUs in the community. This suggests HCV infection risk in serially reincarcerated inmates is higher when they are outside the prison setting.

Screening for HCV is not routine in the corrections setting. Although Varan and colleagues surveyed and received responses from state correctional departments in all 50 states, only 12 reported they had conducted routine HCV screening at least once since 2001. As of the mid-point of 2014, 2 states require HCV screening for inmates. Illinois protocol requires HCV screening for all prison entrants who do not opt out, and New York state law mandates HCV screening be offered to all baby boomers receiving healthcare services.

Data on the rates of HCV-related morbidity and mortality among inmates are also limited and dated. A retrospective cohort analysis of 302 inmates in the Virginia Department of Corrections who underwent liver biopsy in 1998-2002 found 24% had bridging fibrosis or cirrhosis. An analysis of data from male inmates in the custody of the Texas Department of Criminal Justice from 1994 through 2003 found HCV was listed as a cause in 9%, 15% and 33% of deaths (N = 3603) from overall causes, chronic liver disease, and HCC respectively. Over the study period, the HCV mortality rate increased an average of 21% annually.

There are no recent data available concerning the rates of HCV treatment and SVR in the corrections setting. A single study published in 2012 compared the rates of treatment for incarcerated (n = 319) versus nonincarcerated (n = 234) individuals seen at a Wisconsin academic medical center clinic in 2002-2007, finding that ~60% of each cohort were treated and achieved an SVR rate of 38%-43% based on available treatment regimens (Peg-IFN + RBV) at that time. The FBOP 2014 HCV treatment recommendations establish priorities for inmates in more urgent need of intervention, noting that it is reasonable to defer treatment in cases of less advanced fibrosis until the...
Trends in Special Settings (cont.)

Corrections (cont.)

availability of improved treatment options. Clinical scenarios that indicate an inmate should be prioritized to receive therapy include advanced hepatic fibrosis/cirrhosis, receipt of liver transplant, HIV coinfection, and comorbid medical conditions associated with HCV (eg, cryoglobulinemia and certain types of lymphomas). The recommendations also state inmates who were being treated at the time of incarceration should continue therapy. Groups of inmates the FBOP guidelines state are not candidates for treatment include those who: have contraindications to any component of the treatment regimen, are pregnant, do not have sufficient time remaining on their sentence to complete a course of treatment, and do not demonstrate the willingness and ability to adhere to the regimen and to abstain from high-risk activities while incarcerated. Over 90% of incarcerated individuals eventually will be released into the community, emphasizing the importance of providing HCV testing and linkage to care services for those inmates who are not treated while incarcerated.

Knowledge Gaps

The first 4 years of this decade have witnessed a proliferation of research and publications in HCV epidemiology and management. Knowledge gaps remain in several important areas, some of which are touched upon by the results of the HCV Management Trends survey summarized in the next section (see p. 26 for further discussion).

Epidemiology and disease burden: Knowledge among the general public concerning HCV infection remains low. Because most individuals with HCV are not aware they are infected, current prevalence figures may be significant underestimates. Estimates of the rate of advanced fibrosis/cirrhosis in the US HCV-infected population are largely based on modeling data. Also, HCV may be severely underrecorded on death certificates, even for individuals who die from liver-related causes, indicating an underestimate of current US CHC-related mortality. Finally, evidence indicates surveillance rates for HCC in CHC-associated liver disease cases, including patients with cirrhosis who have achieved SVR, are suboptimal.

Screening: HCV screening rates remain suboptimal. Limited evidence is available concerning screening rates in baby boomers or whether the 2012 CDC and 2013 USPSTF Grade B recommendations have increased screening rates in this demographic. There are currently no data available concerning the proportion of HCV screening done via lab-based EIA versus rapid antibody testing. Finally, data are lacking elucidating the impact of HCV screening versus no screening on clinical outcomes and concerning the comparison of the clinical effects of alternative screening strategies (ie, screening in alternate settings, such as in pharmacies or community centers).

Diagnosis: Evidence currently indicates linkage to care is a continuing barrier to CHC-associated liver disease diagnosis (and treatment) in general and especially in underserved or marginalized populations, which are inordinately impacted by HCV infection. No data are available to provide an estimate of the proportion of patients who undergo liver biopsy before treatment. There are also no studies available that have investigated the proportion of HCV-infected patients who undergo noninvasive fibrosis measurements versus biopsy.

Treatment: Gaps exist in the literature concerning which subspecialties of healthcare providers are treating CHC, whether patients are increasingly being treated by primary care providers, the proportion of clinicians’ practices devoted to CHC patients, and the time it takes clinicians to manage a patient with HCV. There are no data available concerning how often any of the available pretreatment tests—whether recommended/indicated or not—are used prior to antiviral HCV treatment initiation or for on-treatment monitoring. There are few data concerning fibrosis severity in patients being treated today or the proportion of patients for whom CHC antiviral treatment continues to be deferred and the reasons for deferral. Also, few studies since 2013 have investigated the proportion of patients treated with specific anti-HCV regimens. Previous estimates indicate HCV treatment rates are low.

Special settings: There is a general lack of evidence on HCV infection in corrections populations. Estimates of the prevalence and burden of infection, as well as of HCV screening, liver disease diagnosis, treatment, and SVR rates among inmates, are based on limited or older studies and surveillance.
HCV Management Trends: Results from a Market Research Survey in the Context of Data in the Literature

This section summarizes key findings from 2 comprehensive surveys conducted among a sample of healthcare providers and managed care professionals and compares their responses with data available in the literature concerning the epidemiology, burden, and management of hepatitis C virus (HCV). In addition, the section includes expert commentary from Editorial Board members to further contextualize the survey findings and provide insight on the factors that may have influenced survey participants’ perceptions of the issues. For some questions, such as HCV prevalence and the estimated rate of infected individuals who remain undiagnosed, responses from healthcare providers (HCPs) and payers either reflected or contrasted with results published in studies. For others, such as the frequency of use of different diagnostic modalities, the proportion of time providers spend managing HCV patients, and the severity of fibrosis in patients being treated today, responses from survey participants begin to fill gaps that are not well addressed by current published research.

Survey Methods
The surveys, which polled respondents about prevailing attitudes, current management, and future outlook on HCV, were conducted under market research conditions. That is, although participants were screened for certain qualifications, including familiarity and experience with HCV, they were not asked to gather additional data from member databases or patient records to inform their answers. As such, responses are based on participants’ own knowledge at the time and, therefore, represent their unaided impressions of the impact of HCV in their members/patients or organizations/practices. The online surveys were conducted in June-July 2014 and took about 30 minutes to complete. Please see the Appendix (p. 60) for a more detailed explanation of survey methodology.

Survey Limitations
Limitations of the survey methodology include:

- Total number of survey participants was limited to 125 healthcare providers and 48 payers
- Smaller sample sizes for some payer groups (corrections, specialty pharmacy provider [SPP], or pharmacy benefits manager [PBM]) do not allow for further segmentation of responses
- Survey participants were compensated by Gilead Sciences, Inc.; however, responses were blinded to those responsible for compiling and analyzing the survey data
- Editorial Board members also were compensated for their participation; however, their views and opinions are their own, and do not necessarily reflect those of their respective employers or companies or of Gilead Sciences, Inc.

Profile of Survey Participants
Surveys were completed by 173 respondents. Of those, 125 were healthcare providers (Table 2, p. 27), comprised of infectious disease specialists, gastroenterologists, hepatologists, and nurse practitioners. Providers who participated in the survey estimated ≥94% of their time was spent seeing patients. About 40% were in private practice in an office setting, 19% practiced in a university setting, 13% were staff physicians in hospitals, 13% were staff physicians in clinics, and 13% were in private practice in hospital settings. A small proportion of healthcare providers (2%) practiced in the Veterans Health Administration (VHA). Providers estimated they saw 381 patients per month on average. Responses were analyzed by specialty and by whether providers practiced as part of an accountable care organization (ACO; 18% of providers) or integrated delivery network (IDN; 23% of providers).
Profile of Survey Participants (cont.)

Forty-eight survey participants represented payer organizations. The payer sample subgroup was designated both by the type of organization (health insurance plan, PBM/SPP, and corrections facilities) and by the professional role of the respondent (pharmacy director, medical director, or case manager; Table 3).

Table 2. Profile of HCP Survey Participants

<table>
<thead>
<tr>
<th>Web Surveys Administered</th>
<th>Completes by Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Infectious disease specialist (ID)</td>
<td>51</td>
</tr>
<tr>
<td>B. Gastroenterologist (GE)</td>
<td>40</td>
</tr>
<tr>
<td>C. Hepatologist (HEP)</td>
<td>24</td>
</tr>
<tr>
<td>D. Nurse practitioner (NP)*</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Web Surveys Administered</th>
<th>Completes by Target Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Accountable Care Org. (ACO)</td>
<td>23</td>
</tr>
<tr>
<td>member</td>
<td></td>
</tr>
<tr>
<td>B. Accountable Care Org. (ACO)</td>
<td>102</td>
</tr>
<tr>
<td>non-member</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
</tr>
<tr>
<td>C. Integrated Delivery Network (IDN)</td>
<td>29</td>
</tr>
<tr>
<td>member</td>
<td></td>
</tr>
<tr>
<td>D. Integrated Delivery Network (IDN)</td>
<td>96</td>
</tr>
<tr>
<td>non-member</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
</tr>
</tbody>
</table>

*Nurse practitioners saw an average of 47 HCV patients per month in 2014.

Table 3. Profile of Payer Survey Participants

<table>
<thead>
<tr>
<th>Respondent Organizations</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health insurance plan (HP)</td>
<td>34</td>
</tr>
<tr>
<td>Pharmacy benefit manager/ Specialty pharmacy provider (PBM/SPP)</td>
<td>8</td>
</tr>
<tr>
<td>Corrections facility pharmacy director/ medical director</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respondent Types</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy director</td>
<td>30</td>
</tr>
<tr>
<td>Medical director</td>
<td>13</td>
</tr>
<tr>
<td>Case manager</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
</tr>
</tbody>
</table>

- Payer respondents rated themselves as very familiar (9 on a scale of 1 to 10) with the process that new pharmaceutical products must go through to gain formulary approval at their organization and with HCV coverage considerations at their organization.
- Less than half of payers (42%) reported they are part of an organization affiliated with an ACO. Of those who were part of an ACO, 90% reported their organizations’ responsibilities include managing HCV.
- More than half of payers (58%) said they work for organizations that are part of an IDN.
- PBM/SPP respondents were more likely to be affiliated with an ACO (88%) and work for an IDN (88%) than health insurance plan respondents (35% and 56%, respectively).

HCV Prevalence and Diagnosis Rates

Estimates of HCV Prevalence

Based on survey results, healthcare providers are seeing an increasing number of patients with HCV in their practices. Payers, however, have mixed perceptions about the change in the rate of HCV diagnosis among their members over the past 2 years. Based on what is known from the literature, payer respondents tended to overestimate HCV prevalence.

- Of healthcare providers surveyed, 68% reported the number of HCV patients they manage has increased over the past 2 years, whereas <2% estimated this patient population has decreased (Figure 7, p. 28).
  - Healthcare providers who are part of an ACO, compared with those who are not, were more likely to say the number of HCV patients they manage has increased—87% vs 64%, respectively.
- Healthcare providers who reported their HCV practice has stayed the same (22%) acknowledged a growth in new patients, but said this was balanced by a loss of other patients due to such factors as death, attrition from nonadherence to appointments (a situation that speaks to the ongoing challenges of maintaining patients under care), and/or a conscious effort on their part to maintain a certain level of patients.
  - Rising mortality in persons with HCV, which increased 9%-13% from 2007 to 2010,66,67 may be contributing to a decline in HCV prevalence in the US.2
HCV Prevalence and Diagnosis Rates (cont.)

Estimates of HCV Prevalence (cont.)

- The mortality rate in persons with HCV is higher than in those without, and persons with HCV die at a younger age than those who are not infected.\(^{67,69}\)

- Although more payers (approximately 38%) reported the HCV diagnosis rate has increased in their plans/organizations over the past 2 years, 33% reported no change, and 29% said they did not know or weren’t sure (Figure 7). Payer respondents who reported an increase in diagnoses cited increased HCV screening rates, as well as the impact of new therapies on raising awareness.

- Payers estimated the current prevalence of HCV among their plans/organization at about 10%. This rate is considerably higher than the Centers for Disease Control and Prevention’s (CDC) estimated prevalence of 1.0%–1.3%, based on the National Health and Nutrition Examination Survey (NHANES), and the 2% estimate from research by Chak et al,\(^3\) based on data derived from sources that included higher-prevalence populations not assessed by NHANES (Figure 8)\(^2,3,27\)

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*The remaining 15 payer respondents (31%) answered ‘don’t know/aren’t sure.’


\(^{2}\)Estimated from an analysis of 52 studies that assessed HCV prevalence in populations not accounted for in NHANES, as well as NHANES 1999-2002 prevalence estimates.
HCV Prevalence and Diagnosis Rates (cont.)

Estimates of HCV Prevalence (cont.)

- Respondents who managed HCV care in corrections facilities estimated about 17% of inmates had HCV, which correlates well with the 12%-35% prevalence estimate in this population from the CDC.

  - The 17% HCV prevalence rate for corrections was nearly double the rate estimated by those whose populations were from health insurance plans (10%) or PBM/SPPs (7%).

- Thirty-one percent of payer survey respondents said they were unaware or unsure of the prevalence of HCV in their members, which may be partially due to the unaided survey methodology and may indicate a need for additional disease education.

Healthcare providers’ estimates of the number of patients they anticipate managing by 2016 are more in line with treatment rate projections available in the literature than payer estimates of management growth.

- In 2014, healthcare providers estimated managing an average of 88 patients with HCV per month. Over the next 2 years, they projected this would grow to an average of 99 HCV patients per month in 2015 (an increase of 12%), and 115 HCV patients per month in 2016 (an additional increase of 16%). In contrast, payers projected the number of members with HCV managed by their plans/organizations would remain flat in 2015 and grow by 3% in 2016 (Figure 9).

  - The most common reason healthcare providers (n = 81) gave for the estimated increase in their HCV patients was better or expanded treatment options. This was cited by 43% of participants who thought they would manage more patients. Other reasons included increased screening (31%), increased diagnosis (24%), and increased awareness (19%) of HCV.

- Hepatologists and infectious disease doctors estimated they currently manage an average of 136 and 92 patients with HCV per month, respectively.

- Gastroenterologists and nurse practitioners estimated they manage 65 and 47 patients with HCV per month, respectively.

- Practitioners in ACOs and IDNs estimated they would continue their current practice of managing more patients with HCV than non-ACO and non-IDN practitioners.

![Figure 9. Comparing HCP and Payer Perceptions of CHC Lives Under Their Management and Care](image)

**Figure 9. Comparing HCP and Payer Perceptions of CHC Lives Under Their Management and Care**

<table>
<thead>
<tr>
<th>Payer Segments</th>
<th>HCV Growth Rates 2015/2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPs (n = 102*)</td>
<td>12% 16% 0% 3% 1% 4% 6% 13%</td>
</tr>
<tr>
<td>Payers (n = 25*)</td>
<td>0% 3% 1% 4% 6% 13% -19% -24%</td>
</tr>
<tr>
<td>HP (n = 18)</td>
<td>1% 4% 6% 13% -19%</td>
</tr>
<tr>
<td>PBM/SPP (n = 3)</td>
<td>6% 13% -24%</td>
</tr>
<tr>
<td>Corrections (n = 4)</td>
<td>4% 6% 13% -19%</td>
</tr>
</tbody>
</table>

*The remaining 23 HCP respondents (18%) and 23 payer respondents (48%) answered “don’t know/aren’t sure.”

HCP survey question: Earlier you indicated that you personally see or treat X number of HCV patients in a typical month. Now please estimate how many HCV patients you expect to be managing in a typical month in 2015. What about in 2016?

Payer survey question: Earlier you indicated that there are X members with HCV in your plans/organization. Now please estimate how many members with HCV you expect your plans/organization to be managing the care of in 2015. What about in 2016?
HCV Prevalence and Diagnosis Rates (cont.)

Estimates of HCV Prevalence (cont.)

- Payer estimates were impacted, in part, by responses from those in the corrections market, who estimate a 19% decrease in HCV diagnoses in 2015 and a 24% decrease in 2016. Payers affiliated with other market segments estimate minimal-to-modest growth in 2015 (1%-6%) and modest-to-moderate growth in 2016 (4%-13%)

- Payer respondents who expected they would be managing more members with HCV predominantly cited increased HCV screening rates as the reason

- A 2014 Health Research Institute (HRI) forecast estimated about 60,000 commercially-insured patients with HCV will be treated in 2014. The report projected this number would rise to just over 80,000 by 2016—an increase of 33%—and then decline gradually each year thereafter.

- The HRI rate is for treatment projections in the commercially-insured population versus overall HCV management projections from the market research survey

Although the unaided survey methodology may have contributed to the high prevalence estimate (10%) from payers, this rate may also reflect the current focus they have on HCV in general. As David Clark, RPh, notes, “Over the last 4 months, they probably have spent a lot more time on this area than almost any other disease category,” a situation that could influence payers’ perception of the potential impact of HCV among their members. Given that 31% of respondents said they were unaware or unsure of this rate, Editorial Board members thought it is also possible that even among these high-profile categories, payers either have not recently looked at these data or are assuming the known rate within their organization is an underestimate of actual HCV prevalence. “We’re not always acutely aware of that information or retain that data when we’re looking—particularly at drug classes. I think it’s difficult for people to remember incidence/prevalence data, especially given the vast number of diseases/conditions and treatments we are dealing with,” says Sherry Andes, PharmD.

The discrepancy between payer (3%) and healthcare provider (30%) estimates of the projected growth in HCV management rates over the next 2 years until 2016 could be due to selection bias. Providers included in the survey estimated they are seeing an average of 88 patients with HCV among an average of 381 total patients (23%) each month. Such experienced HCV treaters are likely to assume an increased patient load to coincide with increased patient identification and treatment over the next 2 years.

Healthcare providers also may have a different perspective than payers on the impact of increased HCV screening on the number of patients they will be managing in the future. Zobair Younossi, MD believes that although 3% growth may be reasonable for 2014-2015, “it may increase substantially with effective screening strategies.” David Clark agrees that increased awareness of HCV could drive more at-risk patients to ask their doctors about screening and treatment. In comparison to HCV provider perspectives, payers may be looking at historical and current HCV awareness and diagnosis levels and, in turn, estimating a greater proportion of patients already under care and a lower rate of growth for diagnosis.

Given the concern among payers that increased HCV screening and awareness could result in a large uptick in treatment rates, Sherry Andes found it interesting that payer survey respondents estimated flat growth in the next year: “The fact that payers did not project much of an increase in their HCV population seems somewhat contradictory to concern over increased screening leading to a rapid ramp-up of treatment rates and, consequently, costs.”

Proportion of HCV Infection that Remains Undiagnosed

There is a considerable gap between payer and healthcare provider perceptions about how many persons with HCV infection remain undiagnosed. The overall estimate of the undiagnosed rate from healthcare providers who see patients with HCV daily in their practices had better concordance with that in the literature. Payer respondents, in contrast, underestimated the proportion of members with HCV who remain undiagnosed.

- Because many individuals with HCV are not aware they are infected, current prevalence figures in the literature may be significant underestimates. In the survey, payers estimated about 15% of individuals with HCV remain undiagnosed, whereas healthcare providers who see patients with HCV daily in their practices had better concordance with that in the literature. Payer respondents, in contrast, underestimated the proportion of members with HCV who remain undiagnosed.

- The estimate from payers is based on responses from only 26 participants: 46% of respondents said they were unaware or unsure of how many of their members with HCV remained undiagnosed. In contrast, all 125 healthcare providers answered this question (ie, 0% responded they were unaware/unsure)
HCV Prevalence and Diagnosis Rates (cont.)

Proportion of HCV Infection that Remains Undiagnosed (cont.)

– Although it is based on a low number of survey participants \( n = 3 \), corrections facility payer respondents’ estimate of undiagnosed HCV infection rate (7%) was less than half that of health insurance plan respondents (17%) and PBM/SPP respondents (15%)

– The perception that 85% of their members with HCV have already been diagnosed could be exacerbating payer concerns about the budgetary implications of a spike in treatment rates

– The higher rate of undiagnosed patients supported by NHANES data and echoed by healthcare providers in the survey indicates any increase in actual treatment rates could be more gradual due to continuing barriers to HCV screening as well as linkage and access to care

• Among healthcare provider respondents, 36% said the percentage of undiagnosed HCV patients has decreased over the past 2 years, mainly because of increased screening and awareness. Only 8% of payers thought the percentage had decreased, although 28% were not sure (Figure 10B)

– Hepatologists (54%) were more likely than infectious disease doctors (28%) or nurse practitioners (10%) to report a decrease in undiagnosed patients

“Payers, in general, are only going to know who’s diagnosed and being treated. They really have no way of knowing how many are potentially on the books that aren’t getting diagnosed or treated; that is going to require modeling.”

– Sherry Andes, PharmD

The proportion of patients with HCV that remains undiagnosed is one of the most important issues that concerns providers and payers alike. Healthcare providers believed this rate to be almost 3 times that estimated by payers. Payers are generalists, managing the care of patients with many different conditions. Sherry Andes, PharmD, also notes that “Payers, in general, are only going to know who’s diagnosed and being treated. They really have no way of knowing how many are potentially on the books that aren’t getting diagnosed or treated; that is going to require modeling.” Providers, especially the specialists included in the survey, have closer proximity to HCV patients, which may afford wider familiarity with the issues.
HCV Prevalence and Diagnosis Rates (cont.)

Proportion of HCV Infection that Remains Undiagnosed (cont.)

“However,” as Brian Pearlman, MD, points out, “healthcare providers were divided on whether or not the proportion of people with HCV that remains undiagnosed has changed in the past 2 years, and 28% of payers were unsure. In other words, no one seems to have a good handle if increased screening is working, and maybe because there are no data on this,” he says. “It is critical to understand if baby boomer screening is working. We need an objective way to monitor the success of screening protocols.”

HCV Infection and Disease Characteristics

Infection Characteristics

Compared with payers, healthcare providers surveyed appear to have a better sense of the prevalence of genotypes (GTs) in persons with HCV infection in the US. Both groups of participants, however, may have underestimated the average duration of infection in persons with HCV.

- Healthcare providers surveyed estimated 67% of their patients with HCV had GT 1, which is slightly under the 70%-78% GT 1 HCV US prevalence rates reported in the literature (Figure 11).28-30 Payer perceptions of GT 1 prevalence among members (48%) were less on par with reported rates. Moreover, 40% of payers (compared with 14% of healthcare providers) indicated they were unsure of genotype distribution among their members, indicating a potential knowledge gap

- Healthcare providers who practiced in a VHA setting said 75% of their patients had GT 1 infection

- Because the peak years of HCV infection in the US occurred in the 1980s,7 it has been estimated that a large proportion of people with HCV have been infected for 25–35 years.15 Of healthcare provider survey respondents, 22% estimated the average duration of HCV infection in their patients to be >20 years; 31% estimated the average duration of infection for their HCV patients was >10 to <20 years (Figure 12, p. 33). In contrast, only 4% and 17% of payer respondents estimated the average duration of HCV infection in their members was >20 years or >10 but <20 years, respectively

- The majority of healthcare providers (53%) reported the average length of time their HCV patients have been infected was ≥10 years, whereas 47% said their patients had been infected for <10 years

- The majority of payers (58%) thought the average duration of HCV infection in their members was <10 years. Only 21% thought their members with HCV had been infected for >10 years

- The majority of payer survey respondents estimated that most HCV patients have been living with the infection for 10 or fewer years, which suggests that they might not fully appreciate or understand the downstream health impact that is imminent among their membership. This misperception may be due to high rates of turnover among health plan membership. As Brian Pearlman, MD, notes, “Providers tend to have a little bit more longitudinal relationship with patients, meaning we’ve had them longer than the managed care organization may have had them under their wings. Providers also have direct patient contact.” Moreover, “the payer is looking across the whole environment” notes David Clark, RPh
HCV Infection and Disease Characteristics (cont.)

Infection Characteristics (cont.)

“When you ask [payers] how long the average patient may have had [HCV], unless they’ve actually worked with a hepatologist or infectious disease doctor on these patients, they are not likely to know.” “Healthcare providers actually see the patients, and understand and, in general, can identify the risks associated with HCV acquisition,” says Zobair Younossi, MD. Payers “tend to become aware of HCV much later than the providers.” Sherry Andes, PharmD, agrees that “a lot of people also don’t know or may not recall the long progression period. They just remember that a lot of these patients don’t exhibit symptoms and, when they do, that’s when they’re having liver impairment.”

- Similar to reports in the literature, 51% of healthcare providers surveyed who responded to the question said injection drug use (IDU) was the number 1 risk factor for infection, accounting for more than half of their patients with HCV (Figure 13). However, provider respondents said the source of infection was unknown in 22% of patients, and 20% of providers selected “don’t know/aren’t sure”

- These data are similar to those from studies that show many HCV-infected persons do not recall or report having any specific risk factors

![Figure 12. Payer and HCP Perceptions of Average Duration of Infection in Individuals with HCV](image)

**Figure 12. Payer and HCP Perceptions of Average Duration of Infection in Individuals with HCV**

<table>
<thead>
<tr>
<th>Duration of HCV infection in years</th>
<th>Payers (N = 48)</th>
<th>HCPs (N = 125*).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsure</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>&gt;20 – &lt;30</td>
<td>14%</td>
<td>30%</td>
</tr>
<tr>
<td>&gt;10 – &lt;20</td>
<td>31%</td>
<td>31%</td>
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<td>&gt;5 – &lt;10</td>
<td>1%</td>
<td>2%</td>
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<tr>
<td>&gt;1 – &lt;5</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>&lt;1</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*HCPs were not given ‘unsure’ as a response option.

Payers (N = 48) HCPs (N = 125*)

![Figure 13. Sources of HCV Infection](image)

**Figure 13. Sources of HCV Infection**

- Known and potential exposures during the 6 months prior to onset of HCV-related illness in 270 patients with acute (new) HCV infection.

*Williams et al, 2011*

*IDU = injection drug use*
HCV Infection and Disease Characteristics (cont.)

HCV Morbidity and Comorbidity

Based on healthcare providers’ responses, the burden of HCV in their patients is considerable. Although healthcare provider responses concerning fibrosis severity rates in their patients help to shed some light on this data gap, a substantial proportion of both providers and payers are not aware of disease progression in HCV patients/members. Healthcare providers also indicated their patients with HCV have a number of comorbidities, including type 2 diabetes mellitus, which has been associated with chronic HCV infection.1

• Estimates of advanced fibrosis/cirrhosis rates in persons in the US with HCV available in the literature are largely based on modeling data.8,42,45,47 In one such analysis, Davis and colleagues42 estimated that in 2010, 42% of individuals with chronic HCV infection had minimal or mild fibrosis (F0/F1) and about 40% had severe fibrosis or cirrhosis (F3/F4). They projected that by 2015, roughly 30% of persons with chronic HCV infection would have cirrhosis. Although the sample size was small (N = 105) and the data were collected using an unaided survey methodology, responses from healthcare provider survey respondents help put some figures behind the projections:

  – Forty-seven percent of patients were estimated to have none or mild fibrosis at the time of presentation (F0, 23%; F1, 24%)
  
  – Eighteen percent were estimated to have moderate fibrosis (F2) and 27% had severe fibrosis (F3) or cirrhosis (F4) (Figure 14)

• However, 24% of healthcare provider respondents either did not know the fibrosis severity in their HCV patients overall or indicated this was the case for a percentage of their patients. This applied to 71% of payer respondents

• Based on the peak years of HCV infection incidence in the US, it has been estimated that cases of advanced fibrosis/cirrhosis are increasing in this population.8,42,45 In the market research survey, 23% of providers reported the percentage of HCV patients with cirrhosis had increased over the past 2 years (Figure 15, p. 35). Only about 10% said cirrhosis prevalence in their patients had decreased, whereas half (50%) reported it had stayed the same

  – Hepatologists reported higher rates of F3/F4 fibrosis in their patients (32%) than reported by other groups (18%-27%), but were more likely to say the rate of cirrhosis in their patients had stayed the same over the past 2 years (67%) compared with other groups (40%-49%)

  – Sixteen percent of healthcare providers said they did not know or weren’t sure about the severity of liver disease in their patients or if the rates of cirrhosis had increased over the previous 2 years

• In concordance with what is known from studies in the literature,6,9,48 factors associated with a more rapid progression of HCV-related liver disease cited by healthcare provider survey respondents included human immunodeficiency virus (HIV)-1 co-infection (75%), duration of HCV infection (68%), high body mass index (BMI; 50%), African-American race (42%), older age at time of infection (39%), and male gender (32%) (Table 4, p. 35). Hepatologists (79%) were more likely than other practitioners (31%-58%) to report that high BMI was a contributing factor to cirrhosis
HCV Infection and Disease Characteristics (cont.)

HCV Morbidity and Comorbidity (cont.)

- Healthcare provider respondents (N = 125) estimated 24% of HCV patients in their practices will progress to liver failure each year if left untreated, which is nearly 4 times the annual rate of progression from cirrhosis to decompensation estimated by Alazawi and colleagues\textsuperscript{58} in their meta-analysis of the literature (6.4%; N = 2386)
  - Hepatologists and nurse practitioners estimated 15% and 37% of their patients, respectively, would progress to liver failure each year if left untreated
  - It is possible HCV patients with cirrhosis managed by provider respondents are closer to liver failure (ie, more ill) than the population as a whole
- About 62% of healthcare providers reported the rate of progression to liver failure has stayed the same over the past 2 years, whereas 22% said it decreased and 16% said it increased. Healthcare providers who indicated the progression rate had stayed the same pointed to the chronic nature of HCV-associated liver disease and the late stage of disease at presentation; those who said it had decreased cited increased and earlier HCV detection, diagnosis, and treatment
  - Among hepatologists, 87% estimated the rate of progression to liver failure had remained steady over the past 2 years compared with 54%-60% of gastroenterologists, infectious disease doctors, and nurse practitioners
- The risk of progression from HCV-related cirrhosis to hepatocellular carcinoma (HCC) has been estimated at about 3.5% annually\textsuperscript{54} and the US incidence of HCC increased 5.4% each year from 2000 to 2007 and 2.3% each year from 2007 to 2010\textsuperscript{59} These data are in line with survey responses from healthcare providers, who estimated 4% of HCV patients in their practices had HCC
  - An analysis of NHANES data found chronic HCV was an independent risk factor for insulin resistance, hypertension, and congestive heart failure\textsuperscript{51} The most common comorbidities in HCV patients of surveyed healthcare providers were depression (27%), steatosis (19%), diabetes (18%), and anemia and cardiovascular disease (16% for each) (Table 5, p. 36)
  - Overall, 15% of patients with HCV in healthcare providers’ practices had HIV-1 co-infection. This proportion was higher for infectious disease doctors (27%) and lower for gastroenterologists (5%)
Forty-six percent of payers expected the rate of liver failure progression to stay the same in their members over the next 2 years, whereas 21% said they were unsure and 21% did not answer the question. The majority of payers (54%) also were unsure about the proportion of members with HCV who will eventually require treatment for cirrhosis, liver failure, HCC, or non-liver–related HCV complications. The 22 payers who responded estimated these proportions at 24%, 19%, 15%, and 17%, respectively.

Payer respondents listed the following as the top comorbidities among their members with HCV: diabetes, 20%; depression, 18%; cardiovascular disease, 17%; and chronic hepatitis B infection, 13%.

Editorial Board members thought that the 24% annual rate of progression to liver failure among HCV patients reported by providers was a gross overestimate. Although this response may be due to a misinterpretation of the question, Brian Pearlman, MD, also thought it could reflect the need for increased education for providers.
HCV Infection and Disease Characteristics (cont.)

HCV Morbidity and Comorbidity (cont.)

“The healthcare community (and the public), with maybe the exception of liver specialists or people who focus on [HCV] all the time, are generally undereducated. That’s why I think education is key.”

Healthcare providers in the survey said 27% of their patients have severe fibrosis or cirrhosis. “Certainly, that is starting to approach a significant number,” notes Michael Ellis, RPh. “All those patients would be ready for treatment now.” In fact, Brian Pearlman believes this percentage could be an underestimate. “The number I’m more familiar with from the landmark modeling study by Davis and colleagues’ published in 2010 is 40% for combined F3 or F4 fibrosis/cirrhosis,” he says.

The proportion that will progress to advanced disease and the time frame of progression are important for payers to know as they attempt to determine the cost/benefit of treatment in terms of future cost offsets. As Deborah Reissman, PharmD, notes, many patients with HCV “may hibernate for decades before they present with any symptomology.” Given budgetary constraints that prevent all HCV patients from receiving therapy at once, payers are looking for guidance concerning the optimal time to treat to prevent progression, especially so as to avoid the need for liver transplantation.

However, based on the large proportion of payers who responded they were unsure of disease progression rate in their members with HCV, payers lack the information needed to make these determinations. Payers are “not necessarily aware of which patients are sitting on liver transplant lists, or which patients have F3/F4 fibrosis. That’s just not data that they see on a daily basis or even a frequent enough basis to have it in the top of their mind,” says Deborah Reissman. “The gastroenterologists and/or hepatologists are seeing these patients frequently and have a much better idea as to how many patients are at the various stages of disease progression.”

Payers tend to focus on HCV liver-related outcomes, which are the most obvious sequelae and the easiest to measure. As providers’ responses concerning comorbidities illustrate, however, the impact of HCV extends to other areas as well. Zobair Younossi, MD, explains: “The [non-liver-related] outcomes were more difficult to, first of all, appreciate, and then to measure. For example, diabetes is associated with HCV, but how many of all diabetics in the US have HCV, and how many of these patients had their diabetes aggravated by HCV infection? It’s probably a small proportion of all diabetics. On the other hand, a substantial proportion of patients with HCV will report chronic fatigue. The question is: How do you actually quantify that and how do you connect it to the HCV?

“Curing the HCV improves overall mortality, not just liver-related mortality.”

— Brian Pearlman, MD

Nevertheless, considering the extrahepatic manifestation of HCV certainly adds to the complexity of HCV infection and its true clinical and economic burden.” Looking at the impact of HCV on all-cause mortality, suggests Dr. Brian Pearlman, is one way to bring home to payers the importance of comorbidities in patients with HCV. “Curing the HCV improves overall mortality,” he notes, “not just liver-related mortality. This illustrates that there’s likely something extrahepatic that’s happening to worsen death rates.” Cure is in the best interest of all patients.”

“[Payers are] not necessarily aware of which patients are sitting on liver transplant lists, or which patients have F3/F4 fibrosis. That’s just not data that they see on a daily basis or even a frequent enough basis to have it in the top of their mind. The gastroenterologists and/or hepatologists are seeing these patients frequently and have a much better idea as to how many patients are at the various stages of disease progression.”

— Deborah Reissman, PharmD
Screening and Diagnosis

Screening and Linkage to Care

Healthcare provider survey respondents recognized the need to increase HCV screening rates and the gap in linkage to care, especially in underserved or marginalized populations, illustrated by data in the literature. Their responses also echo results of the CDC analysis of data from the Chronic Hepatitis Cohort Study (CHeCS), which suggested that, in addition to increasing testing in physicians’ offices, other locations might be important for increasing the number of HCV-infected persons who are screened and referred to care.

- The most common step taken by healthcare providers to reduce the rate of undiagnosed HCV was to encourage PCPs to screen for HCV and to refer HCV-positive patients for management (78%; Table 6). Providers also cited increased risk-based (61%) and baby boomer birth cohort–based (59%) screening activities. Only 8% said they had not changed their HCV screening practices.

  – Providers who were part of an ACO were more likely to report encouraging screening and referral in PCPs and increasing risk-based screening than non-ACO healthcare provider respondents.

- The top 3 community activities healthcare providers thought would most effectively increase HCV diagnosis rates were the following: screening in community-situated (eg, churches, sexually transmitted disease/methadone facilities) clinics and referral for care (66%); government-supported HCV awareness campaigns (46%); and state- or federally-mandated HCV testing (38%).

- On average, both healthcare providers and payers thought the Affordable Care Act (ACA) has been “somewhat impactful” on making HCV screening a part of routine clinical practice in appropriate age and at-risk patient populations. Zobair Younossi, MD, commented that he believes ACA will have a positive impact on HCV screening “when HCV screening becomes a core measure for closed systems, outpatient practices, or ACOs.”

- One of the barriers to linkage to care for patients with HCV infection is lack of a referral to see a specialist. In the market research survey, 53% of healthcare providers surveyed reported the number of patients with HCV referred to their care has increased in the past 2 years; 37% said this number has stayed the same (Figure 16, p. 39). Only about 2% reported a decrease.

  – Healthcare providers reported that about 69% of their HCV patients were referred to them, and 31% were diagnosed by them.

- A higher percentage of payers (21%) said they had not implemented any programs to increase HCV diagnosis rates, perhaps because they estimated only 15% of their members with HCV were undiagnosed.

- Overall, payers estimated their organizations were “somewhat likely” (6 on a scale of 1 to 10) to engage in HCV awareness programs in the next 2 years. About 40% said this was extremely likely, while 19% said this was not at all likely.

Forty-two percent of payer survey participants said the most common tactic they had implemented to improve HCV diagnosis rates among members was a targeted awareness campaign (eg, high-risk, baby boomer cohorts); 33% said they had implemented awareness and education initiatives for physicians. However, David Clark, RPh, believes that although payers may have increased HCV-related communications to providers, in his experience, the materials have largely concerned treatment coverage policies rather than increasing screening or awareness. Deborah Reissman, PharmD, agrees, noting “This survey seems to suggest that there is a lot more general screening happening than what I am seeing.” Payer responses, therefore, may have been skewed by how they interpreted the question.
Screening and Diagnosis (cont.)

Screening and Linkage to Care (cont.)

One of the data gaps identified in the literature concerned the proportion of HCV screening done via lab-based enzyme immunoassays (EIA) versus point-of-care rapid antibody testing. Limited evidence also is available concerning whether the 2012/2013 CDC and US Preventive Services Task Force (USPSTF) recommendations have increased screening rates in baby boomers.

- Eighty percent of healthcare providers surveyed reported they use lab-based antibody tests followed by tests confirming active HCV viremia to screen patients; 59% said they incorporated liver function tests (LFTs) in their screening protocols.

- Eighty-three percent of payer respondents reported their organizations covered EIA for HCV screening.

Provider respondents indicated continued reliance on lab-based HCV screening tests, which were covered by more payers than the point-of-care rapid antibody test. Rapid antibody testing is anticipated to be used by more and more providers, however, because of the small amount of blood needed and the positive impact of having results available within minutes on linkage to care. As Zobair Younossi, MD, explains, “A test that will take a few days to come back will represent a bit of a challenge for linking the patient to care. On the other hand, if you have a test that you get the results back within a few minutes, you can link that patient to care more efficiently and immediately.”

— Zobair Younossi, MD
Screening and Diagnosis (cont.)

Diagnosis

The frequencies with which clinicians use biopsy, transient elastography, and other tests when diagnosing HCV-related liver disease and determining treatment course was another data gap in the literature that the market research survey responses from healthcare providers began to address (Figure 17). Healthcare providers surveyed report a continued reliance on biopsy but also a growing use of transient elastography to assess HCV-related liver damage. Although providers and payers generally agree HCV RNA and liver function testing should be done prior to initiating antiviral therapy, there are some differences in perceived protocols. This may be due to differences in how the questions were worded on the groups’ surveys, but also might reflect an opportunity for improved coordination.

- Of providers, 81% and 26% said they used liver biopsy and transient elastography, respectively, to determine the severity of HCV-related liver disease. Other commonly used diagnostic tests were LFTs (67%), complete blood count (CBC) (54%), and hemoglobin/hematocrit tests (27%)

- Providers most often used genotype testing (74%) to determine the course of HCV treatment (Table 7, p. 41). Other tests included LFTs (66%), HCV RNA level testing (64%), and CBC (57%)

- Fifty-five percent and 14% said they used liver biopsy and transient elastography, respectively, to determine the course of HCV treatment

- Providers who were part of an ACO were more likely to use LFTs and HCV RNA testing (both 83%) than non-ACO provider respondents (60%-62%)

- Providers reported they used LFTs, HCV genotype, and RNA level testing to guide treatment course for 80% or more of patients. In comparison, biopsy and transient elastography were used to guide therapy in 50% and 39%, respectively, of patients

- Nearly three-quarters (72%) of healthcare providers said they expect to increase their use of transient elastography over the next 2 years to guide decisions about the course of HCV treatment. One third said they expected to decrease their use of biopsy, whereas 41% said their use of biopsy would stay the same

- At least half of payers said their organizations required lab-based HCV antibody testing, HCV genotype testing, and LFTs for treatment initiation in their members (Table 6). Only 27% and 17% of payer respondents said their plans required liver biopsy or transient elastography, respectively

N = 125.

HCP survey questions: When you are determining the severity of HCV-associated disease in patients, which tests do you use? Select all that apply. For each of the tests you selected in the previous question, please indicate the percentage of patients for which you would use that test in order to make treatment decisions. For each option input a percentage between 1 and 100%. For each of the tests you selected in the previous question do you expect the impact on HCV treatment decisions within your practice to increase, decrease or stay the same over the next 2 years? Please select the best response.

Figure 17. Trends in the Use of Biopsy vs Transient Elastography

<table>
<thead>
<tr>
<th>Test</th>
<th>Current Practice</th>
<th>Over Next 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>81%</td>
<td>20%</td>
</tr>
<tr>
<td>Transient elastography</td>
<td>55%</td>
<td>72%</td>
</tr>
<tr>
<td>CBC</td>
<td>26%</td>
<td>33%</td>
</tr>
<tr>
<td>HCV RNA level testing</td>
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<td>6%</td>
</tr>
<tr>
<td>LFTs</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Complete blood count</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin/hematocrit tests</td>
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<td></td>
</tr>
</tbody>
</table>

GILEAD
Screening and Diagnosis (cont.)

Diagnosis (cont.)
The overwhelming majority of healthcare providers surveyed continue to rely on biopsy, but the majority believe noninvasive methods of assessing liver disease severity, such as transient elastography, will become increasingly important. As more providers gain access to the new technologies, Brian Pearlman, MD, believes questions about the need for biopsy will continue to arise. “I think there will always be some role [for biopsy],” he says, “but where it fits into the diagnosis process will increasingly be an issue.”

HCV Management and Treatment

Scope of HCV Management
Healthcare provider survey participants were experienced HCV treaters and reported the management of HCV accounts for a substantial and growing proportion of their practices. Which healthcare providers (eg, hepatology vs infectious disease) are treating CHC, the proportion of clinicians’ practices devoted to HCV patients, and information concerning on-treatment testing were all gaps identified in current research that were addressed to some extent by their responses.

• Healthcare providers reported that 29% of their practice currently is devoted to HCV management. In line with the growth of patients with HCV in their practices, half of healthcare providers reported this has increased over the past 2 years, 42% said it has stayed the same, and only 2% reported it has decreased

• Based on the proportion of time the respondents estimated they devoted to HCV patients (42%), hepatologists (n = 24) are the primary treaters of HCV (Figure 18)
  – Nurse practitioners (n = 10) and infectious disease doctors (n = 51) may also be important treaters of HCV, as those surveyed indicated they spend 33% and 31% of their time, respectively, managing patients with HCV
  – Gastroenterologists surveyed (n = 40) estimated 19% of their practice is devoted to management of patients with HCV

• The market research survey did not poll PCPs. The proportion of patients with HCV being treated in primary care practices remains a gap

<table>
<thead>
<tr>
<th>Test/Procedure</th>
<th>% HCPs Who Use Test to Determine Treatment Course (N = 125)</th>
<th>% Payers Who Require Test Prior to Treatment Initiation (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype testing</td>
<td>74%</td>
<td>52%</td>
</tr>
<tr>
<td>LFTs</td>
<td>66%</td>
<td>50%</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>64%</td>
<td>35%</td>
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<tr>
<td>CBC</td>
<td>57%</td>
<td>35%</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>55%</td>
<td>27%</td>
</tr>
<tr>
<td>Hemoglobin/hematocrit</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td>IL28B</td>
<td>32%</td>
<td>15%</td>
</tr>
<tr>
<td>Lab-based HCV antibody test</td>
<td>27%</td>
<td>54%</td>
</tr>
<tr>
<td>Q80K</td>
<td>21%</td>
<td>17%</td>
</tr>
</tbody>
</table>

HCP survey question: When determining the course of treatment for your patients with HCV, which tests do you use?
Payer survey question: What is required by your plans/organization for initiation of HCV treatment in your member population?
HCV Management and Treatment (cont.)

Scope of HCV Management (cont.)

• Providers follow up with HCV patients who are being monitored but not yet treated approximately 6 times each year, with hepatologists and nurse practitioners seeing these patients ≥7 times per year. Patients who are receiving treatment are seen roughly once each month (12 times per year), with hepatologists and infectious disease doctors reporting more frequent follow-up visits (15 times per year for each group)

– VHA healthcare providers indicated they see patients they are monitoring but not yet treating 3 times per year compared with 7 times per year for those who are receiving treatment

• Fifty-two percent of payers responded on-treatment monitoring is required for therapy continuation; 29% said they require no on-treatment monitoring; and another 19% were unsure

Healthcare respondents estimated that nearly one-quarter of their practice was devoted to managing HCV. This rate could reflect a bias in the sample towards very experienced and active HCV treaters or, as Brian Pearlman, MD, speculates, it could be artificially inflated. “Perhaps their perception is that HCV is difficult to manage, so they overemphasize or overestimate how much of their day they spend managing HCV patients. It may also be all the time and effort they have to spend getting therapy approved for patients.”

A sizeable minority (37%) of healthcare providers said they had not observed an increase in patients referred to them over the past 2 years. Brian Pearlman agrees: “In my practice and some others, I have not seen a large acceleration in referrals.” However, just over 50% of survey respondents reported increased referral rates, which may be a reflection of increased screening on the part of providers, increased awareness among patients, or other factors.

Payer respondents who required on-treatment monitoring indicated its purpose was primarily to assess effectiveness and compliance. Zobair Younossi, MD, and Brian Pearlman agree that a proportion of providers also use on-treatment HCV RNA monitoring primarily to assess patient regimen adherence and effectiveness. “It’s how you follow patients,” says Brian Pearlman. “Even if you trust the patient to be 100% adherent, you need to assess if therapy is doing what it’s supposed to do. Is it suppressing the virus?” He also believes on-treatment testing can be used to provide patients with encouragement that the treatment regimen is working.

HCV Treatment Rates

The rate of patients being treated, as well as treatment success rates, are important pieces of information payers need to manage HCV pharmacy budgets. Healthcare providers and payers largely agreed on the proportion of persons with HCV currently being treated among their patients/members, but quoted considerably higher rates than those reported in the literature.

• Analysis of NHANES and other study data estimate only 16% of individuals with chronic HCV initiate treatment (Figure 19, p. 43). Payers who responded to the question(403,539),(445,590) (n = 34/48) estimated 47% of their members with HCV currently are being treated, whereas 53% are being monitored but are not being treated with pharmacotherapy. Healthcare providers estimate they are currently treating 41%, and are monitoring about 38%, of their HCV patients. Another 21% of patients in providers’ practices have undergone antiviral treatment in the past but have ongoing HCV infection and are not currently undergoing therapy (deferral rate = about 59%)

– Providers were not asked to estimate the percentage of treatment-naïve versus treatment-experienced patients with HCV in their practices, but rather to divide patients into being treated, not yet treated, and treated but with continued ongoing infection

• VHA healthcare providers estimated only 21% of their HCV patients are actively being treated. This proportion is higher than the 12% treatment rate in veterans estimated by Kramer et al156 but was closer to the data available in the literature than the treatment rates reported by non-VHA providers and payers

– Providers in the VHA reported that 57% of their patients are being monitored but not yet treated, and 22% have undergone treatment in the past but have ongoing HCV infection

This disconnect could reflect a bias in the cohort of payer and healthcare provider survey respondents, who self-selected as being either very familiar with HCV coverage considerations at their organization or managing a high number (88 on average) of HCV patients per month, respectively. It could also indicate a new trend of increased treatment rates over those in the past. However, given the unaided survey methodology, it is also possible that survey participants believed more patients with HCV were initiating treatment than actually are.
HCV Management and Treatment (cont.)

HCV Treatment Rates (cont.)

One surprise was the proportion of patients who had failed previous HCV therapy, and were now being monitored but were not undergoing treatment (21%). As Michael Ellis, RPh, notes, “I was expecting [healthcare providers] were deferring treatment more for treatment-naïve patients. I was surprised that a fairly high number had been previously treated.”

There are few data in the literature concerning fibrosis severity in patients being treated today or the proportion of patients for whom CHC antiviral treatment continues to be deferred and the reasons for deferral.

- Healthcare providers estimate that 52% and 47% of their patients with F3 fibrosis and F4 cirrhosis, respectively, are treated today (Figure 20); 40% and 45% of patients with F1 and F2 fibrosis, respectively, are being treated today.
HCV Management and Treatment (cont.)

HCV Treatment Rates (cont.)

- Just over one third (36%) of healthcare providers reported they use liver function/fibrosis/biopsy to determine whether to treat now or to defer treatment for their patients with HCV. Patients’ willingness/compliance/preference and comorbidities/stability were determining factors for 22% and 20% of respondents, respectively (Figure 21, p. 45).

- Aside from the introduction of new treatments, the top reasons healthcare providers gave for deferring HCV antiviral therapy for patients were patient out-of-pocket costs (38%), patient refusal (36%), the presence of comorbidities that preclude treatment (34%), and patient lack of insurance coverage for desired therapy (26%).

- Similarly, when asked why patients choose to defer HCV antiviral therapy, aside from the introduction of new treatments, healthcare providers cited patient refusal (36%), out-of-pocket costs (35%), lack of insurance coverage for desired treatment (30%), and the presence of comorbidities that preclude treatment (26%).
  - Infectious disease doctors and nurse practitioners selected patient refusal (45%-50%) more often than hepatologists and gastroenterologists (21%-30%).

- More than half (54%) of healthcare providers anticipate that the proportion of their deferred treatment population will decrease over the next 2 years, primarily citing the availability of new therapies.
  - Sixteen percent reported it will increase, and 14% reported it will stay the same. Those who said it would increase or stay the same pointed to potential issues with access to new therapies.
  - Non-ACO providers were (19%) more likely than providers in ACOs (4%) to project an increase in HCV treatment deferral rates over the next 2 years.

The substantial rate of patient refusal of HCV therapy (36%) reported by providers is striking and may be due to a number of factors. Because people with chronic HCV infection may not have any symptoms, they may not believe they need treatment even if they are aware of having the infection. In addition, psychosocial factors (eg, stigma) may play a role in patients’ refusing therapy for HCV more than for other disease states. According to David Clark, RPh, “One [reason patients refuse treatment], of course, is that they don’t accept that they have a problem. Another is they don’t accept that there’s really any way to be better. The third is they’re not willing to tolerate the side effects or the costs [of treatment]. It’s a problem in any disease state, whether it is diabetes or asthma—getting patients to take seriously what they have and knowing that they can be better.” Healthcare providers and professionals need to be aware of the potential impact of this issue on HCV treatment rates and emphasize that HCV can be cured.

Factors Influencing Treatment and Coverage Decisions

Payers and healthcare providers agree on the importance of considering recommendations from expert associations and public health authorities, as well as input from colleagues/peers, in making HCV treatment decisions. For the most part, providers noted characteristics of therapies as influencing treatment decisions, whereas payers also factored in the cost-effectiveness of treatments.

- On average, healthcare providers reported being somewhat familiar (7 on a scale of 1 to 10) with the recent American Association for Study of Liver Diseases/Infectious Disease Society of America (AASLD/IDSA) guidance for HCV treatment and also thought they were very impactful on how they treat HCV (8 on a scale of 1 to 10).
  - Overall, 46% considered themselves extremely familiar with the guidance and 60% rated them extremely impactful (scores of 8-10).
  - Seventy-five percent of hepatologists considered themselves extremely familiar compared with 30%-41% of providers in other specialties.

“One [reason patients refuse treatment], of course, is that they don’t accept that they have a problem. Another is they don’t accept that there’s really any way to be better. The third is they’re not willing to tolerate the side effects or the costs [of treatment]. It’s a problem in any disease state, whether it is diabetes or asthma—getting patients to take seriously what they have and knowing that they can be better.”

— David Clark, RPh
HCV Management and Treatment (cont.)

Factors Influencing Treatment and Coverage Decisions (cont.)

- Payers reported a similar level of familiarity with the AASLD/IDSA guidance as healthcare providers (6 on a scale of 1 to 10) but considered them only somewhat impactful on formulary decisions (7 on a scale of 1 to 10)
  - PBM/SPPs reported a higher level of familiarity and placed more emphasis on the recommendations than other payers: 63% were very familiar and said they were very impactful versus 29%-35% and 33%-44% for other providers, respectively

- In addition to AASLD/IDSA recommendations, 44% of payers chose other HCV guidelines, such as those from the European Association for the Study of the Liver (EASL) or the World Health Organization (WHO); 31% chose recommendations from government agencies; and 27% cited colleagues/peers among their top 3 other important sources of information for guiding HCV treatment decisions (Figure 22, p. 46). Healthcare providers chose colleagues/peers (55%), society-sponsored learning events (39%), and other HCV guidelines (34%) among their top 3 important sources of information

- Sustained virologic response (SVR) is very important (9 on a scale of 1 to 10) for healthcare providers in choosing a treatment regimen. Almost all—92%—of hepatologists rated SVR as very important compared with 85% of gastroenterologists, 78% of infectious disease doctors, and 60% of nurse practitioners

- Excluding SVR, healthcare providers had mixed responses on other factors that influence choice of HCV antiviral treatment regimens, with no factor garnering more than 15 out of 100 points. The top 3 factors were tolerability (ie, side effects, ease of use; 14 points), guideline-recommended regimen (13 points), and safety (ie, drug–drug interactions; 12 points)

- Similarly, no single feature predominated payers’ responses on what factors influence HCV treatment coverage decisions. Cost-effectiveness of the regimen received the most points (16 out of 100), and payers allocated 13 points to cost/SVR. Other factors were efficacy across multiple genotypes (10 points), guideline-recommended regimen (9.5 points), and level of patient adherence (9 points)
  - Respondents who managed HCV care in corrections facilities assigned 26 points to cost/SVR and 20 points to level of patient adherence

- On average, both healthcare providers and payers thought the ACA has been “somewhat impactful” on HCV management approaches
HCV Management and Treatment (cont.)

Factors Influencing Treatment and Coverage Decisions (cont.)

Although providers (8 out of 10) placed slightly more emphasis on the AASLD/IDSA guidance than payers (7 out of 10), the concordance in their responses concerning familiarity with the guidance and other sources informing treatment/coverage decisions has positive implications for patient management coordination. In general, as Zobair Younossi, MD, notes, updated guidelines from other organizations, including those from EASL and VHA, have been consistently similar in their recommendations; this has served as “confidence validation” for the guidance by professional societies.

When asked what factors motivated their choice of therapy aside from SVR rates, payers and healthcare providers gave somewhat different answers. Although both cited guideline recommendations as important factors, providers focused on the tolerability and safety of therapy, whereas payers emphasized cost-effectiveness and cost/SVR. Deborah Reissman, PharmD, notes that payers tend to focus on cost-effectiveness because it “includes outcomes, safety, tolerability, cost—all rolled into one.” She and Sherry Andes, PharmD, agree that, setting aside cost-effectiveness, payers (like healthcare providers) would also consider tolerability and safety to be the next most important factors. Deborah Reissman believes “Cost should not be the only driver of what regimens should be used. Rather, the regimen chosen should be the best regimen for that patient considering all of the variables.”

“Cost should not be the only driver of what regimens should be used. Rather, the regimen chosen should be the best regimen for that patient considering all of the variables.”

— Deborah Reissman, PharmD
HCV Management and Treatment (cont.)

Future Trends Affecting HCV Management

No single trend rose to the forefront as being the most important factor influencing the future of HCV management: both payers and providers thought many different drivers would come into play. However, when specific factors were grouped together, treatment attributes (eg, higher cure rates with regimens) were seen as most influential by providers, whereas payers thought environmental factors (eg, emergence of quality measures) would have more influence.

- In allocating points across different future trends (Figure 23), healthcare providers assigned an average of 50 out of 100 points to treatment attributes (eg, efficacy, tolerability, duration), whereas payers assigned 10 fewer points, on average, to this category of factors

- Payers considered environmental factors (eg, increased screening and treatment rates) to be slightly more important influencers on future management trends than treatment attributes, assigning the former 43 points and the latter 40 points, on average

  - The most important environmental factors for payers were emergence of quality measures for HCV management (7 points), patient adherence (7 points), and use of integrated care teams to manage members with HCV (6.5 points)

  - Healthcare providers assigned only 37 points on average to environmental factors, the most important of which were significant increases in HCV screening (8.5 points) and treatment (7 points) rates

- Increases or decreases in treatment costs were seen as having a similar potential to influence future HCV management trends by both groups, with payers assigning a slightly higher average number of points (about 17) to these factors compared with healthcare providers (about 13)

  - Corrections respondents allocated 2- to 4-times the average number of points (20) to increased cost of HCV treatment compared with health plan (8) and PBM/SPP (5.5) respondents

Cost Considerations

Patient cost burden of treatment was a concern for healthcare providers; however, payer reimbursement was less of a factor in their treatment decisions.

- According to healthcare providers, cost of therapy, chosen by 22%, is the number 1 burden faced by patients with HCV, followed by side effects of therapy (21%) and the psychological (16%) and physical (15%) impact of HCV-associated disease

- Sixty-four percent of healthcare providers, citing concerns over access and adherence, said patient out-of-pocket costs were very impactful on their treatment decisions. Hepatologists (75%) and infectious disease doctors (71%) were more likely than gastroenterologists (48%) to consider this factor very important

- However, payer reimbursement was less of a factor influencing healthcare provider choice of regimen, receiving only 9 out of 100 points

![Figure 23. Trends with Greatest Impact on HCV Management in the Next Few Years](image)
Cost Considerations (cont.)

These results illustrate a high level of concern among healthcare providers for patient burden of costs. “If you have a co-pay or coinsurance of several thousand dollars—which, by the way, is not terribly unusual—that’s a significant burden. We need to help these patients get past that,” said Michael Ellis, RPh. He notes there is a need to connect patients with foundations, support programs, and other sources to help mitigate this impact: “Many times, payer reimbursement is not so much the hurdle as it is patients’ ability to pay their portion.” The low importance of reimbursement noted by respondents, however, was surprising for Brian Pearlman, MD, who thought it could be an artifact of the regional distribution of healthcare providers who participated in the survey. Although all regions were represented, fewer respondents were located in the Southeast, Southwest, and West (38%) than in the Midwest and Northeast (62%). “There are certain regions of the country where [reimbursement] is not as important, and there is less of a managed care impact,” he notes.

“If you have a co-pay or coinsurance of several thousand dollars—which, by the way, is not terribly unusual—that’s a significant burden. We need to help these patients get past that.”

– Michael Ellis, RPh

Payers are increasingly managing HCV and estimate increases in pharmacy budgets for HCV therapies in the near term. Considering treatment costs in the context of SVR rate reflects a more complete estimate of a plan’s investment in a patient’s treatment.150,152,153 Based on payer survey responses, cost-effectiveness and cost/SVR calculations for antiviral therapy appear to have increasingly more influence on HCV management decisions. It appears, however, as if payers lack access to essential information and processes to make meaningful comparisons.

- Half of payer respondents reported organizational efforts/resources devoted to managing HCV have increased over the past 2 years, whereas only 4% and 17%, respectively, thought their efforts have decreased or stayed the same. Payers (n = 20/47; the remaining 27 answered “don’t know/aren’t sure”) estimated that HCV treatments represent about 19% of their overall pharmacy budget for 2014, a proportion that will increase to 22% in 2015 and 2016
- Perhaps because of the market research conditions under which the survey was administered, which did not allow payers to research costs in their systems before answering questions, 42% and 67% did not know or were not sure, respectively, of the per-member annual pharmaceutical and non-pharmaceutical costs for managing HCV
- Those who were knowledgeable estimated annual per-member pharmaceutical costs at about $206,000 (n = 28) and non-pharmaceutical costs at about $681,500 (n = 16)
- Pharmaceutical and non-pharmaceutical cost estimates were much lower for corrections ($167,000 and $5,000, respectively), and non-pharmaceutical cost estimates were higher for health plans ($896,600)
- Eighty-one percent of respondents who answered the question included lab monitoring requirements in their non-pharmaceutical cost estimate. Other costs mentioned were physician office visits (69%), hospitalization (63%), emergency department visits (50%), and biopsy or other tests to evaluate liver disease severity (31%)
- Although just under half (46%) of payers reported that HCV regimen cost-effectiveness has increased in importance over the past 2 years, only a quarter of respondents said they had compared HCV regimens based on cost-effectiveness. The remaining 75% of payers either did not know or said they had not conducted such a comparison. About half of respondents (52%) said their organizations have plans to evaluate HCV regimens based on cost-effectiveness

- Payer respondents selected “reduced cost of therapies to patients (co-pay or cost share)” (60%) as their greatest unmet need concerning medications for treating HCV
Cost Considerations (cont.)

- Although 60% of payers indicated “total cost (pharmacy + medical)/SVR” was one of their top 3 relevant measurements of HCV regimen cost-effectiveness, only 38% of respondents reported their plan/organization had the data capability to capture members with HCV who achieved SVR with treatment.

- One quarter of payers said their plans/organizations could not capture these data, and 38% answered “don’t know/aren’t sure.” Health plans were considerably more likely (44%) than corrections care organizations (17%) to be able to capture these data.

- Respondents who indicated they had the data capability to capture SVR rates in their members cited electronic medical record systems and case management as tools to accomplish this task.

- Other measures of cost-effectiveness were “pharmacy-related costs/total pharmacy budget” (56%) and “pharmacy-related costs/SVR” (44%). Only 27% of payers indicated “total cost/QALY” (quality-adjusted life-year) was a relevant measure of cost-effectiveness.

Payers who responded to the question estimated that HCV therapy costs accounted for almost one-fifth (19%) of their pharmacy budgets, with the significant caveat, however, that 57% of the payer survey participants were unsure of this ratio. Because the survey asked for unaided responses, this high percentage is likely a perception on the part of respondents, who are reacting to the increased attention HCV therapy costs have received. David Clark, RPh, comments that payers “just know there are a lot of patients or a lot of demand. They’re not sure where it will boil down to.” Notes Michael Ellis, RPh, “If you look at just specialty pharmacy trend in general, HCV is not the biggest cost driver in my experience.” The 19% estimate “just seems incongruent with what other data say about payer awareness of their own HCV population based on my experience,” he adds.

Cost-effectiveness ranks as the most important factor impacting HCV coverage, but only 25% of respondents said their plans have compared the cost-effectiveness of HCV treatment regimens. This discrepancy could be because of data access and gathering constraints within organizations. Unlike what exists with more prevalent chronic conditions, such as asthma or diabetes, the availability of data is not as robust for HCV. Bottlenecks that can occur with requests for data also are problematic. “Getting a special report request in the queue,” notes Deborah Reissman, PharmD, is a challenge to payers who want to analyze cost-effectiveness. “Resources are focused on routine and required reporting. Special reports like this are much more difficult to get in a quick turnaround time.” As David Clark put it, “The [information technology] resources are going to what is regulated, as well as what affects reimbursement. There have been so many competing priorities for payers in the last 10 years that it’s a challenge to get the right resources to deal with all the things you want to do clinically.”

“Everybody talks cost-effectiveness; not everybody knows how to measure or calculate it,” notes David Clark. More than half of payers considered cost of HCV therapy in the context of the total pharmacy budget as a way to measure cost-effectiveness. “Plans are focused on the cost of the drug itself or drug regimens themselves, the cost per day or cost per treatment course and when it is an outlier in their pharmacy budget. Most plans are not looking at the overall cost of managing patients with this disease,” says Deborah Reissman. According to David Clark, PBMs especially are focused on the cost of medications because they do not have access to other data that factor into the total treatment costs or the costs of failure to treat HCV. Health plans, on the other hand, have a better ability to understand the medical costs, such as lab tests, office visits, and hospitalizations, which PBMs do not see.
Cost Considerations (cont.)

“When you take the payers’ perspective, then you’re going to talk about the pharmacy budget perspective, primarily. This approach only focuses on the cost of medication and neglects the cost of remainder of care. In my view, it is the cost of “cure” that is important. As more and more systems emphasize chronic disease management and bundled payments, I suspect our approach is going to change,” says Zobair Younossi, MD. Based on payer responses, “total cost (pharmacy + medical)/SVR” is also a relevant measure of treatment cost-effectiveness. This metric can account for patients who need either dose reductions or additional drugs added due to adverse events (AEs) or who have to stop treatment due to AEs, which can add to the cost of treatment beyond the price of the initial therapeutic regimen. Cost/SVR can also account for health state costs. Zobair Younossi notes, “For the past 25 to 30 years, we focused primarily on HCV as a liver disease. We have to move away from that and emphasize that HCV is a systemic disease with both liver and non-liver manifestations.” Non-liver-related outcomes also are relevant in terms of measuring the impact of not treating HCV, which is top-of-mind for payers when determining the cost-effectiveness of treating HCV in general. “We don’t have really good long-term outcome data. We don’t know what the recurrence rate or reinfection rates are,” says David Clark. Michael Ellis notes, “In theory, over the long haul, you’re going to actually eliminate the opportunity for [disease] costs. It is important payers understand the total cost of care, the treatment options, and where those buckets are—meaning transplant to hospitalizations, all the different places they’re spending on these diseases.”

“In theory, over the long haul, you’re going to actually eliminate the opportunity for [disease] costs. It is important payers understand the total cost of care, the treatment options, and where those buckets are—meaning transplant to hospitalizations, all the different places they’re spending on these diseases.”

— Sherry Andes, PharmD

In some cases, the availability of medical data to determine the outcomes of treatment can confound payers’ efforts to determine cost-effectiveness of HCV treatment/therapeutic regimens. Less than 40% of respondents reported their plan/organization had the data capability to capture members with HCV who achieved SVR. “They may not ever actually see a post-treatment SVR without requesting it from the physician or auditing the medical record to get it. Unless it is required for continued therapy, it is not something the plan can easily obtain,” says Deborah Reissman. “Pharmacy claims are more timely,” agrees Sherry Andes, PharmD, “whereas medical data takes a while to get.” According to David Clark, “Most payers today require lab results to be shared with them digitally, so it can go into some type of a record. That doesn’t mean [their] systems are set up to use it. Because HCV was not in the top 10 to 20 things that were followed, it’s just not something that they have tried to capture or use.” The effects of SVR on long-term outcomes are also difficult for health plans to measure in their members.
Case Management and Role of Specialty Pharmacy

Payers who responded to questions about case management approaches for members with HCV emphasized the importance of adherence to therapy. Payers who anticipated changes in case management approaches over the next few years indicated increased focus on “cost control and therapy adherence” and “more intricate management.” About half of payers thought member counseling on HCV (54%) or adherence programs (51%) were case management activities that will increase in importance. Nearly half—49%—thought the use of integrated care teams would increase, and 42% thought member educational materials would increase in importance.

Providers and their support staff are the primary “cheerleaders” to increase patient adherence to HCV antiviral therapy, but payers can use case management to take a more active role. According to Deborah Reissman, PharmD, however, case managers “are more likely to work with patients going for transplant, but may not get involved with the patient before that.”

Several payer respondents indicated they use the case management capabilities of network specialty pharmacies, through which members are given “one-on-one personal attention” or are “contacted at least once a month.” As David Clark, RPh, notes, SPPs and PBMs “do have to show that they’re adding value to their clients or customers in helping them understand what’s really happening.” Michael Ellis, RPh, agrees that SPPs “can supplement providers’ lack of resources with their hepatitis experience.” For high-volume practices, according to Brian Pearlman, MD, SPPs are invaluable resources for helping with prior authorization. The payer survey participants who were PBMs or SPPs (n = 8, 4 of whom answered the question) estimated that HCV represents between 19% and 20% of their business. Among this subgroup of payer respondents:

• A majority (about 63%) provided insurance verification as a service to members with HCV
• Half (50%) ensured prior authorization requirements are met for treatment initiation/continuation
The ACO Perspective

Compared with non-ACO-affiliated providers, providers who were part of an ACO:

• Managed more patients with HCV per month in 2014 (73 vs 155)
• Anticipated they would be managing more patients per month in 2016 (91 vs 208)
• Were more likely to say the number of HCV patients they have managed over the past 2 years has increased (64% vs 87%)
• Were less likely to say HCV treatment deferral rates in the past 2 years had increased (19% vs 4%)

“I think ACOs are concerned about quality and total cost of care [which may explain why] they would be trying to get these patients to be treated sooner rather than later.”

— Sherry Andes, PharmD

Providers and payers affiliated with an ACO “own the patient from the entire spectrum of their diseases” rather than “managing only an aspect of the patient’s disease,” according to Zobair Younossi, MD, and have a better understanding that “postponing [HCV] treatment…is going to just increase costs later on because they may have to cover liver transplant or liver cancer.” Deborah Reissman, PharmD, notes, “ACOs … by definition are looking at total cost of care, are more in tune with their total population, are focusing on higher cost populations, [and] probably are more aware of what’s going on in this disease state [HCV] than the non-ACOs. ACOs are incentivized financially to manage high costs [patients] and improve quality.” Zobair Younossi and Deborah Reissman also agree that an ACO is more conducive structurally to care pathway implementation and clinical integration among specialties, which can ensure more efficient delivery of services to HCV patients. “I think ACOs are concerned about quality and total cost of care,” says Sherry Andes, PharmD, which may explain why “they would be trying to get these patients to be treated sooner rather than later.”
Summary of Similarities and Differences in Payer and HCP Responses

There were a number of questions included on both surveys to which payers and healthcare providers provided similar responses/estimates (Table 8):

- Payers and healthcare providers estimate that 41%-47% of patients/members with HCV currently are undergoing treatment.
- Of HCV patients/members, 27%-33% are estimated to have severe fibrosis/cirrhosis.
- AASLD/IDSA guidelines are rated as being of similar impact to treatment and coverage decisions (7-8 on a scale of 1-10).
- Both groups think higher cure rates of HCV treatment regimens will have the greatest impact on future management trends (11%-12%).

Table 8 (p. 54) summarizes questions for which payers and healthcare providers had divergent perceptions. In general, payers and healthcare providers differ in their estimations of the scope of HCV, as well as their unmet needs in terms of managing HCV:

- Payers estimate 15% of members with HCV remain undiagnosed, whereas healthcare providers estimate 42% of persons with HCV are undiagnosed.
- Payers and healthcare providers project a 3% and 28% increase, respectively, through 2016 in the number of members/patients with HCV they will be managing.
- Aside from SVR, healthcare providers say level of tolerability is the most important factor in choosing a treatment regimen; for payers, it is cost-effectiveness.

Some of these discrepancies can be attributed to the different perspectives of payers and providers. “I definitely think the difference in what was the most important factor for a prescriber versus a payer wasn’t too surprising. One can expect payers would be more interested in the cost of care as the top concern, whereas a provider usually tends to focus on something more related to the patient, such as tolerability,” notes Sherry Andes, PharmD.

### Table 8. Summary of Similarities in HCP and Payer Responses

<table>
<thead>
<tr>
<th>Topic</th>
<th>HCPs (N = 125)</th>
<th>Payers (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% responding that undiagnosed HCV population has increased</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Estimated % of HCV patients/members currently treated</td>
<td>41%</td>
<td>47%</td>
</tr>
<tr>
<td>Estimated length of time patients/member had HCV infection</td>
<td>47% of patients infected &lt;10 years</td>
<td>58% of patients infected &lt;10 years</td>
</tr>
<tr>
<td>% of HCV patients/members with severe fibrosis/cirrhosis</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>% of HCV patients/members with diabetes comorbidity</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>% of HCV patients/members with depression comorbidity</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>Use/approval of lab-based HCV antibody test followed by quantitative polymerase chain reaction (PCR) or p-deoxyribonucleic acid (pDNA), if warranted</td>
<td>80% say they use to screen</td>
<td>83% say approved for screening</td>
</tr>
<tr>
<td>Average rate of impact of AASLD/IDSA guidance changes</td>
<td>8 out of 10</td>
<td>7 out of 10</td>
</tr>
<tr>
<td>Trend with greatest future impact</td>
<td>Higher cure rates of HCV treatment regimens (11%)</td>
<td>Higher cure rates of HCV treatment regimens (12%)</td>
</tr>
</tbody>
</table>
Conclusion

Overall, healthcare providers who participated in the survey appeared to have a better understanding of the scope of HCV burden and management versus payers. Sherry Andes offered a potential explanation for this, stating: “This type of information isn’t always available in one place. It requires analysis of medical, pharmacy, and lab data; some of these data are more readily available than others. Some of the key data points require more in-depth analysis or external research that may require assistance from analytic or clinical personnel.”

Key areas where there was some concordance between provider responses and data in the literature included the proportion of persons in the US with GT 1 infection, the importance of IDU as a risk factor for infection, and the factors associated with a more rapid progression of HCV-related liver disease. Healthcare provider perceptions about the duration of HCV infection in their patients, the proportion of persons with HCV who remain undiagnosed, and the projected increase in HCV treatment/management rates were more in line with the available data than payer responses. However, healthcare providers seemed to overestimate the annual rate of progression to liver failure in their patients. There was some concordance between payer and CDC estimates of HCV in the corrections population, but in the general population, payers appeared to have overestimated HCV prevalence. Both healthcare providers and payers appeared to overestimate the proportion of patients with HCV being treated.

Table 9. Summary of Differences in HCP and Payer Responses

<table>
<thead>
<tr>
<th>Topic</th>
<th>HCPs (N = 125)</th>
<th>Payers (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients/members with HCV who remain undiagnosed</td>
<td>42%</td>
<td>15%</td>
</tr>
<tr>
<td>% responding that HCV diagnosis/management has increased</td>
<td>68%</td>
<td>38%</td>
</tr>
<tr>
<td>over past 2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of HCV patients/members with GT 1</td>
<td>67%</td>
<td>48%</td>
</tr>
<tr>
<td>Use of HCV genotype testing to confirm course or required</td>
<td>74%</td>
<td>53%</td>
</tr>
<tr>
<td>to initiate treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average growth in HCV patients/members being managed in 2015</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Average growth in HCV patients/members being managed in 2016</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Most important factor besides SVR rate in decision to use</td>
<td>Level of tolerability</td>
<td>Cost-effectiveness of regimen</td>
</tr>
<tr>
<td>or cover a particular HCV regimen</td>
<td></td>
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</tr>
</tbody>
</table>

Summary of Similarities and Differences in Payer and HCP Responses (cont.)

One of the key themes that emerged from survey respondents was the apparent knowledge gap between healthcare providers and payers. The high proportion of payers who responded “don’t know/aren’t aware” to questions came as somewhat of a surprise (Table 10, p. 55). With all of the press and talk around this category, said Deborah Reissman, PharmD, “it gives the impression that organizations are tracking this pretty closely.” Perhaps because they are closer to patient management issues, healthcare providers were more confident in their ability to provide informed opinions than payers. Sherry Andes adds, “There is a lack of information that payers and healthcare professionals have at their fingertips. Maybe that parleys back into the fact that we don’t have electronic medical records or other technologies that could assist us in having this information more readily retrievable and recallable. I think getting down to the details is difficult, since probably most of these medical directors, pharmacists, and prescribers are so busy with administrative and patient-directed work that they may not be able to keep up with trends.”
Remaining gaps in the literature that were not touched upon by survey respondents include:

- Impact of HCV screening versus no screening on clinical outcomes
- The time it takes clinicians to manage a patient with HCV
- The proportion of patients with HCV managed/treated by primary care physicians
- Rates of liver disease, HCV screening, treatment, and SVR in corrections populations

Future issues of the Gilead *Hepatitis C Trends Report* will track how healthcare provider and payer perceptions of the burden, diagnosis, and management of HCV change over time, and will also address remaining gaps in current knowledge of HCV.
References


73. References

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References (cont.)


To establish a complete understanding of hepatitis C virus (HCV) management, Ogilvy CommonHealth Market Access, a healthcare consultancy and research firm commissioned by Gilead Sciences, Inc., developed and fielded 2 comprehensive market research surveys to healthcare providers and managed care professionals concerning their perspectives and practices in HCV management. The following key stakeholder groups were represented:

• Managed care organization pharmacy/medical directors
• Specialty pharmacy providers (SPPs)
• Pharmacy benefits managers (PBMs)
• Case managers
• Correctional health pharmacy/medical directors
• Gastroenterologists
• Hepatologists
• Nurse practitioners specializing in HCV management
• Infectious disease specialists
• Veterans Health Administration (VHA) healthcare providers

Respondents from these various settings and specialties were selected based upon their ability to meet a set of role-specific prequalifying criteria. Payers were evaluated on the following qualifications:

• Representing a national or regional health plan, PBM, SPP, or correctional health organization
• Representing an organization with multiple lines of business (managed Medicaid, managed Medicare, commercial, or corrections)
• Having an interest in or experience with HCV disease management

Healthcare providers were evaluated on the following qualifications:

• Spending more than 50% of their professional time in clinical practice
• Board certified or eligible for board certification
• Currently seeing or treating 50 or more HCV patients
• Has written 5 or more HCV prescriptions in the past 3 months
• Has been in active practice for 2–25 years
• Is not affiliated with any pharmaceutical company or other healthcare manufacturer involved in HCV treatment, including serving as a clinical investigator, consultant, research or other paid service provider

The survey objectives were to:

• Assess who is being treated today, why patients are being deferred, how HCV is currently being managed, and how this will change in the future
• Identify if recent HCV market events have changed payer and HCP activities relative to HCV management
• Identify which future HCV market events might impact activities relative to HCV management and market access
• Determine any material differences between physicians and payers, as well as the impact of affiliations with Accountable Care Organizations (ACOs) or Integrated Delivery Networks (IDNs) on HCV management trends

Sections in the healthcare provider survey contained questions about:

• Respondent background (ie, number of patients with HCV managed per month)
• Assessment of the undiagnosed HCV patient population
• HCV incidence, prevalence, and patient profile
• HCV screening and diagnostic practices
• Impact of HCV treatment guidelines
• HCV treatment practices

Sample subgroups were designated by specialty, ACO member versus non-member, IDN member versus non-member, and practicing at a VHA facility.

Sections in the payer survey contained questions on:

• Respondent background (ie, familiarity with HCV coverage considerations)
• Profile of members with HCV
• Managing the treatment of HCV patients
• Impact of HCV treatment guidelines
• Impact and management of HCV costs
• Corrections- and PBM/SPP-specific issues

Sample subgroups were designated by health insurance plan, PBM/SPP, and corrections. Small sample size precluded designating PBMs and SPPs into different subgroups.

The final survey sample was comprised of 125 healthcare providers and 48 payers from all regions of the US (Northeast, Southeast, Midwest, Southwest, and West). The survey was conducted online in June-July 2014. Each survey took approximately 30 minutes to complete, and participants were compensated for their time. Participants did not know the questions ahead of time and, therefore, did not have an opportunity to research responses in medical records, claims databases, or other sources of information within their organizations. As such, responses reflect unaided perceptions on trends. Responses were blinded to those responsible for compiling and analyzing the survey data.

Editorial Board members reviewed the results of the quantitative research and provided expert commentary on the results in a series of one-on-one telephone interviews conducted in July-August 2014. Although Editorial Board members were compensated for their participation, their views and opinions are their own, and do not necessarily reflect those of their respective employers or companies or of Gilead Sciences, Inc.