According to the CDC, 3.2 million seropositive Americans are living with chronic hepatitis C, 75% of which are baby boomers infected in the 1960’s and 1970’s.¹ Presently, most people become infected with HCV by sharing needles or other forms of injectables.⁵ Injection drug use accounts for 60% to 80% of HCV infection in the United States.⁶ Additional sources of HCV transmission include blood transfusion as well as activities potentially involving percutaneous exposures to infected blood such as tattooing and acupuncture. Vertical transmission of HCV infection is also possible, more than 1 in every 20 children delivered by HCV chronically infected women are infected.⁷ Importantly, the transmission of HCV among household contacts and through sexual contact is also possible.

While testing for HCV on newly infected people is important, it is imperative for people from the baby boomer generation. It is estimated that baby boomers constitute the majority of the approximately 15,000 Americans who die from HCV-related liver disease annually.¹ Moreover, this number is expected to increase exponentially in future years. The CDC estimates that the testing of baby boomers could identify over 800,000 additional people with hepatitis C, and could potentially save more than 120,000 lives.⁸ The adoption of preventive measures, timely detection, and appropriate treatment of HCV infection is critical to contain the hepatitis C epidemic and improve outcomes. The success of a therapy relies on a proper diagnosis and genotyping of the virus. HCV infection is associated with six major genotypes (1 to 6), each with multiple subtypes. The geographic distribution of hepatitis C appears to be dependent upon the virus genotype.⁹ Genotypes 1, 2 and 3 and their subtypes have a global distribution. HCV subtypes 1a and 1b are the most common genotypes in the United States.
States constituting 80% of all HCV infections. These subtypes are also predominant in Europe. The infection of intravenous drug users in the United States and in Europe appears to be caused by the genotype 3a. Genotypes 4, 5 and 6 appear to be prevalent in North Africa and the Middle East, South Africa and Hong Kong, respectively. HCV genotypes are important epidemiologic markers and the heterogeneity of HCV appears to influence the outcome of HCV infection and the response of HCV to therapy. Studies revealed that genotype 1 is the most difficult HCV infection form to treat. These patients are less likely to have a favorable response to interferon treatment with or without ribavirin than are those infected with genotype 2 or 3.

It is very important to understand that unlike many viral infections, hepatitis C is curable. The success of a therapy is indicated by the rate of the sustained viral response (SVR). The SVR is fully achieved when HCV-RNA are undetectable in the serum of patients 12 to 24 weeks after completion of therapy. Presently, a number of drugs are licensed for the treatment of HCV infection: standard interferon (Infergen®, Roferon-A®, Intron-A®, Alferon N Injection®); PEGylated interferon alpha (Pegasys®, Peg-intron®, Sylatron™); ribavirin (Copegus®, Virazole®, Rebetol®, Ribasphere®); three HCV protease inhibitors – telaprevir (Incivek®), boceprevir (VICTRELIS®, Merck) and simeprevir (Olysio™); a nucleotide analog polymerase inhibitor, sofosbuvir (Sovaldi®); and the fixed-dose combination ledipasvir-sofosbuvir (Harvoni™). These drugs are associated with various degrees of efficacy as well as distinct safety profiles, utilization management requirements and costs.

Landscape of Hepatitis C Treatment
The standard of care for patients with HCV infection has changed considerably over the past decades. It shifted from a simple regimen of interferon in 1996 to a dual therapy combining PEGylated interferon alpha (PEG-IFN) and ribavirin in 2002. The PEG-IFN/ribavirin combination was successful in eradicating the virus in approximately 50% of hepatitis C patients. However, the high rate of adverse events and poor tolerability led to the development of more specific, more efficacious therapeutic agents like the direct-acting antiviral (DAA) agents. The latter have proven to be safer and more effective than the dual-therapy regimen, and represent a greater possibility of curing patients who previously failed the other therapies or were ineligible for standard treatment with PEG-IFN/ribavirin. DAA agents target proteins that are essential to the development and replication of the virus. They include NS3/4A proteases inhibitors, NS5B polymerase inhibitors and NS5A phosphoproteins inhibitors.

Boceprevir (VICTRELIS®, Merck) and telaprevir (Incivek®, Vertex Pharmaceuticals) were the first oral protease inhibitors to make it into clinical practice. A triple therapy regimen combining boceprevir or telaprevir, along with PEG-IFN and ribavirin became the standard of care for genotype 1 HCV infection in 2011. In clinical trials, the addition of boceprevir or telaprevir to PEG-IFN and ribavirin significantly increased SVR rate up to 63 to 75%, and shortened the treatment duration in naïve, relapsing, and partially responding patients. However, triple therapy with boceprevir or telaprevir has some major drawbacks including severe adverse events, drug-drug interactions and viral resistance. The subsequent commercialization of new and improved DAA agents – simeprevir (Olysio™, Janssen Pharmaceuticals) and sofosbuvir (Sovaldi®, Gilead Sciences), led the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) to revise the guidelines for testing, managing and treating hepatitis C. As a result, the triple therapy combining telaprevir or boceprevir with PEG-IFN/ribavirin is no longer recommended for the treatment of HCV infection. Additionally,
Vertex Pharmaceuticals, Inc., the maker of telaprevir, recently announced the discontinuation of its product as of October 16, 2014. In November 2013, the FDA approved simeprevir, a second-generation protease inhibitor for use in patients with genotype 1b HCV infection when co-administered with PEG-IFN and ribavirin. The triple therapy yielded SVR rate of 80% in clinical trials. Presently, a daily regimen consisting of 150 mg of simeprevir for 12 weeks along with PEG-IFN/ribavirin for 24 to 48 weeks is an alternative regimen for treatment-naïve patients with either HCV genotype 1b, HCV genotype 1a (without the Q80K polymorphism), or HCV genotype 4 infections. Adverse effects of simeprevir include rash, photosensitivity, and hyperbilirubinemia. The risk of resistance excluded the use of simeprevir in patients who have failed boceprevir or telaprevir based therapies. Simeprevir cannot be used to treat hepatitis C patients co-infected with HIV.

Although simeprevir offers greater treatment options for hepatitis C patients, polymerase inhibitors have shown much potential. These drugs bind to NS5B polymerase to inhibit replication of the virus and can potentially act against all HCV genotypes. In December 2013, sofosbuvir was the first NS5B polymerase inhibitor to be FDA-approved for treating hepatitis C patients regardless of the virus genotype. In clinical trials, sofosbuvir achieved an overall SVR of 90% measured 12 weeks after completion of therapy, without increasing the side effect profile beyond PEG-IFN/ribavirin. Fatigue and headache are the most common adverse events reported with sofosbuvir in combination with PEG-IFN/ribavirin or ribavirin alone. Per the current clinical guidelines, the standard of care for treatment-naïve patients with genotype 1, 4, 5 or 6 HCV infection consists in a daily dose of sofosbuvir (400 mg) with PEG-IFN/ribavirin for 12 weeks. The first line therapy for patients with genotype 2 or 3 HCV infections is a combination of daily sofosbuvir (400 mg) and ribavirin for 12 or 24 weeks, respectively. A double therapy with sofosbuvir (400 mg) and ribavirin is recommended for interferon-ineligible patients with genotype 4 HCV infection. Sofosbuvir offers treatment options to a larger population of hepatitis C patients including:

- Hepatitis C patients who are not eligible to receive interferon;
- Hepatitis C patients previously treated with boceprevir or telaprevir, afforded by the drug high barrier to viral resistance;
- Hepatitis C patients co-infected with HIV as the drug has minimal interaction with anti-retroviral agents; and
- Hepatitis C patients with hepatocellular carcinoma and awaiting liver transplantation.

The pharmaceutical pipeline for hepatitis C treatment is growing at an unprecedented rate. Since January 2014, two DAA agents and two fixed-drug combinations have been submitted for FDA approval. On October 10, 2014, the FDA approved ledipasvir-sofosbuvir (Harvoni™, Gilead Sciences), the first fixed-dose combination therapy, for the treatment of chronic hepatitis C genotype 1 in both treatment-naïve and treatment-experienced patients. In clinical trials, once-daily ledipasvir-sofosbuvir resulted in 94% SVR in eight weeks, and 94% to 99% SVR in 12 weeks among patients with genotype 1 HCV infection. Importantly, these rates were achieved without the need for interferon injections or ribavirin. Prior treatment history and the presence of cirrhosis dictate the duration of therapy; which can range from as little to eight weeks to 24 weeks. Importantly, the simplification of treatment regimen is critical in improving the rate of medication adherence among hepatitis C patients. Thirteen additional novel entities are currently in Phase II or Phase III of clinical
development (Table 1). Multiple clinical trials are ongoing to evaluate the efficacy and safety of various multi-class combination hepatitis C therapies (Table 2). The ultimate goal is to develop interferon-free regimens that are highly effective, associated with fewer adverse events and minimal drug interactions, rely on daily dosing and require shorter duration of therapy and daily dosing, and decrease the pill burden.

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Manufacturer</th>
<th>Therapeutic Class</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasabuvir (ABT-333)</td>
<td>AbbVie</td>
<td>Non-nucleoside NS5B polymerase inhibitor</td>
<td>Under FDA Review</td>
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<tr>
<td>Daclatasvir (BMS-790052)</td>
<td>Bristol-Myers Squibb</td>
<td>NS5A inhibitor</td>
<td>Under FDA Review</td>
</tr>
<tr>
<td>ABT-450</td>
<td>AbbVie</td>
<td>NS3/4A protease inhibitor</td>
<td>Phase III</td>
</tr>
<tr>
<td>Mercitabine (RG6128)</td>
<td>Roche</td>
<td>Nucleoside NS5B polymerase inhibitor</td>
<td>Phase III</td>
</tr>
<tr>
<td>Ombitasvir (ABT-267)</td>
<td>AbbVie</td>
<td>NS5A inhibitor</td>
<td>Phase III</td>
</tr>
<tr>
<td>GS-5816</td>
<td>Gilead Sciences</td>
<td>NS5A inhibitor</td>
<td>Phase III</td>
</tr>
<tr>
<td>MK-8742</td>
<td>Merck</td>
<td>NS5A inhibitor</td>
<td>Phase III</td>
</tr>
<tr>
<td>Ledipasvir (GS-5885)</td>
<td>Gilead Sciences</td>
<td>NS5A inhibitor</td>
<td>Phase III</td>
</tr>
<tr>
<td>Danoprevir (RG7227)</td>
<td>Roche</td>
<td>NS3/4A protease inhibitor</td>
<td>Phase II</td>
</tr>
<tr>
<td>Setrobuvir (RG7790)</td>
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<td>Non-nucleoside NS5B polymerase inhibitor</td>
<td>Phase II</td>
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<tr>
<td>GS-9451</td>
<td>Gilead Sciences</td>
<td>NS3 protease inhibitor</td>
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</tr>
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<td>ABT-072</td>
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<td>Phase II</td>
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<tr>
<td>ACH-3102</td>
<td>Achillion Pharmaceuticals</td>
<td>NS5A inhibitor</td>
<td>Phase II</td>
</tr>
<tr>
<td>Sovaprevir (ACH-1625)</td>
<td>Achillion Pharmaceuticals</td>
<td>NS3/4A protease inhibitor</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
Table 2: Fixed-Dose Combinations Hepatitis C Treatment under Clinical Development

<table>
<thead>
<tr>
<th>Fixed-Dose Combination</th>
<th>Manufacturer</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-267 / ABT-450/r</td>
<td>AbbVie</td>
<td>Under FDA Review</td>
</tr>
<tr>
<td>Sofosbuvir / GS-5816</td>
<td>Gilead Sciences</td>
<td>Phase III</td>
</tr>
<tr>
<td>MK-5172 / Mk-8742</td>
<td>Merck</td>
<td>Phase III</td>
</tr>
<tr>
<td>ABT-493 / ABT-530</td>
<td>AbbVie</td>
<td>Phase II</td>
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**Novel Hepatitis C Therapies: A Challenge to Payers**

The shift to triple therapy resulted in a significant increase in the cost of treating HCV infection. New HCV therapeutic agents are more effective, safer, easier to administer and requires less monitoring. However, the price of these drugs represents a major caveat as it may limit treatment access. A 12-week treatment with sofosbuvir is associated with a wholesale acquisition cost (WAC) price of $84,000. The addition of PEG-IFN and ribavirin to the treatment regimen yields an overall cost of $94,078, which is doubled for a patient with genotype 2 or 3 HCV infection.25 A treatment regimen consisting of simeprevir, PEG-IFN and ribavirin costs $86,516 if administered for 24 weeks, and $106,673 for 48 weeks.26 The fixed-dose combination ledipasvir-sofosbuvir therapy is associated with costs of $63,000, $94,500 and $189,000 if administered for eight, 12 and 24 weeks, respectively.27

The commercialization of high-cost hepatitis C drugs is not without precedent. Based on current WAC prices, the cost of former standard of care consisting of telaprevir or boceprevir, with PEG-IFN and ribavirin ranges from $64,825 to $106,468, depending on the duration of therapy.26 Importantly, these costs do not include additional services such as diagnostics, viral load lab monitoring, assessment of adherence and adverse events, as well as education on drug, disease and side effect management, that are critical to optimize the treatment regimen and manage the condition.

While the new hepatitis C drugs are not the most expensive therapies in the marketplace, their pricing triggered concerns from payers, government officials, and patient advocacy groups. The affordability of these drugs, along with patients’ access to these life-saving medications are key issues raised by these stakeholders. With the rapid emergence of innovative and costly prescription drugs, a crucially needed national debate to address these complex questions has arisen.

The consternation over the price of new hepatitis C drugs stemmed primarily from the size and the nature of the patient base for which these drugs are destined. The majority of hepatitis C patients are baby boomers, individuals that are uninsured or receive health benefit coverage through government programs such as Medicare, Medicaid, the Department of Veterans Affairs or through the prison system. The release of various reports assessing the costs of treating HCV infection with these new hepatitis C drugs
fueled the hepatitis C debate. For example, a report estimated that the cost of new HCV drugs, simeprevir and sofosbuvir, will increase 2015 Medicare Part D spending by approximately $2.9 billion to $5.8 billion, causing Medicare Part D beneficiary premiums to rise by $481 million to $935 million.\(^\text{28}\) This study, like many others, did not depict the full picture of hepatitis C economics. Key elements such as applicable manufacturers rebates and discounts, a clear estimate of the size of eligible hepatitis C patient population, and the impact of a curative treatment on long-term health care costs are not accounted for. When considering the long term cost implications of hepatitis C, it is critical to understand and factor in the medical costs attributed to drug and disease-related complications such as liver cirrhosis and liver cancer.

Hepatitis C patients, especially baby boomers, are heavy users of healthcare resources. Between 2001 and 2010, HCV patients were responsible for 2.29 million outpatient visits, 72,000 emergency room visits and 475,000 inpatient admissions. The total annual cost of inpatient care for hepatitis C patients was over $15 billion.\(^\text{29}\) A recent study showed that the total cost of treating HCV infection is estimated at $6.5 billion and that it will peak in 2024 at $9.1 billion.\(^\text{30}\) Liver transplant can reach a cost of $577,100.\(^\text{31}\) Thus, curing a hepatitis C patient with a $94,078 treatment will likely result in a considerable reduction of medical costs in the long run. Additionally, ensuring that hepatitis C patients are tested and treated with the most cost effective medicine regimens will help contain the epidemic, reducing the incidence and overall cost of HCV infection. To achieve this, it is critical to address the barriers hindering patients’ access to effective hepatitis C treatments.

Payers and purchasers are implementing various strategies to contain hepatitis C-related healthcare expenditures. This is achieved primarily by lowering the price of pharmaceuticals through manufacturers rebates, contracting aggressive discounts and utilizing narrow network strategies like an exclusive Specialty Pharmacy network, as well as limiting the level of drug utilization through prior authorization.

The Price of Hepatitis C Drugs
Managed care organizations (MCO) and purchasers commonly turn to contractual agreements to secure better pharmaceuticals prices. Bulk purchasing, discounts and rebates count among the approaches used by payers to obtain lower drug prices from pharmaceutical manufacturers. Many elements influence the level of rebate negotiated with pharmaceutical manufacturers. These include the uniqueness and effectiveness of the drug, the bargaining power of the payer or pharmacy benefit managers (PBM), as well as the type of formulary the drug will be placed on. The majority of private payers negotiate rebate discounts through their PBMs, allowing them to leverage PBMs’ bargaining power.

Public payers such as the federal and state governments have implemented various programs to contain the cost of pharmaceuticals. Among these, the Medicaid Drug Rebate Program whereby pharmaceutical manufacturers enter into a national rebate agreement with the Secretary of the Department of Health and Human Services (HHS) in exchange for state Medicaid coverage of most of the manufacturer’s drugs. Presently, Medicaid receives a 23.1% rebate discount for all innovator drugs including sofosbuvir and simeprevir.\(^\text{32}\) The Department of Veteran Affairs can also obtain lower prices from manufacturers in exchange for placing manufacturer’s products on its national formulary. Gilead Sciences offered a 44% discount on sofosbuvir to the Department of Veterans Affairs.\(^\text{33}\) Additional programs such as the 340B Drug Pricing Program can bring the price of
key drugs, including specialty drugs, to about 49% of the list price.

Outcomes-based contracting is gaining popularity amongst payers. This approach relies on a pricing model that focuses on clinical outcomes and includes risks. Clinical outcomes are tied to a set of measurable performance standards specific to a drug. Outcomes-based contracting allows for a closer alignment of objectives between the payer and the drug manufacturer, ultimately resulting in better outcomes for patients and cost savings for payers. However, payers and drug manufacturers are facing many challenges in successfully implementing an outcome-based strategy. Clearly defining the desired outcomes and the related key metrics is critical to manage performance and develop a financial model that drives quality.

**Drug Utilization Management**

The most common tool utilized to manage drug utilization, including hepatitis C therapies, is prior authorization which is a process whereby certain criteria set by the insurer must be met before a drug is covered for a member. Generally, prior authorization criteria align with FDA recommendations and clinical guidelines. In the case of new hepatitis drugs, a physician must consider a plethora of factors to determine clinical appropriateness and support optimal outcomes. These factors include HCV genotype, viral levels, past treatment history, therapy outcome (relapse, null responder, partial responder), interferon eligibility status, applicable genetic polymorphisms, liver fibrosis/cirrhosis stage, renal impairment, transplant status, current non-HCV therapies and co-morbidities including co-infection with HIV.

Payers are strengthening the criteria to limit the utilization of the drug and control costs. In the case of hepatitis C drugs, some insurers are prioritizing treatment-experienced hepatitis C patients who did not respond to previous therapies while others set the priority based on stage of liver damage. At the other end of the spectrum are certain Medicaid-contracted health plans refusing to offer the treatment to their Medicaid population. These plans negotiated their contracts before these drugs have been FDA-approved and covered by the states.

**Conclusion**

The rapid advances in the field of hepatitis C resulted in the development of more effective yet more costly drugs. It is critical for private insurers, PBMs and federal and state governments to address the new economics around treating HCV infection in order to cure patients and contain the epidemic. The introduction of costly and innovative hepatitis C therapies is becoming a trend payers must be prepared to manage and mitigate. Warehousing patients that are currently untreated in anticipation of the launch of cheaper therapeutics may exacerbate the problem. There is no one-size-fits-all solution to managing high-cost drugs. A robust strategy should target multiple elements such as formulary and utilization management, price, distribution and site of service. Because the characteristics of each disease state and drug vary, strategies must be developed at the drug level. To that end, a deep understanding of the drivers of drug utilization and cost trends is essential. Comprehensive clinical programs are critical components of these strategies to ensure that the appropriate level of coordination, follow-up and monitoring for patients who have been prescribed specialty pharmaceuticals.

If you would like to learn more about how to manage these trends, Optimity Advisors has the practical knowledge and experience to guide your organization. Our Pharmacy Advisory team
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Dr. Kadija Abounit has over 10 years of experience in the health care industry spanning biomedical research, regulatory affairs, and managed care. She has proven ability to combine scientific knowledge and business practices to collaborate across organizational business units to identify, design and implement strategies to control costs and improve health outcomes. Kadija’s areas of expertise include developing clinical programs and strategies for Specialty Pharmacy and Medication Adherence improvement, designing and leading research projects, developing managed care pharmacy services (e.g., Fraud Waste and Abuse and pharmacy audits, Managed Care Pharmacy workshop for Pharmaceutical companies). She earned a PhD in Pharmacology from Wayne State University and a MBA from Loyola University Maryland.

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