MILLIMAN WHITE PAPER

# Analysis of prescription drugs for the treatment of hepatitis C in the United States

A study of the evolution of second-generation direct-acting antivirals to treat hepatitis C virus from mid-2014 to mid-2020

*Commissioned by Gilead Sciences, Inc.*

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## Executive Summary

Sovaldi®, a direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV), made headlines in the U.S. markets with an average wholesale acquisition cost (WAC) of $1,000 per day, or $84,000 for a 12-week course of treatment. Sovaldi's launch kicked off the second generation of DAAs for HCV, which expanded more widely tolerable treatment options to patients, including increased potential toward HCV elimination for the first time. At the time of launch in 2013, many U.S. payers were concerned with managing existing budgets to accommodate an influx of patients at this price. New therapies further expanded treatment options to an even broader population with HCV and encouraged price competition. In this report we analyzed how cost, utilization, and value assessments have evolved over the past several years for HCV DAAs.

*This report discusses the reduction in cost per treatment regimen from $84,000 in 2013 to an average net cost of approximately $11,500 to $17,000[1] in mid-2020, based on available data across key segments and products.*

We focus our analysis on the following key findings:

- The gross cost of HCV DAAs (measured by WAC) has decreased on average from $1,000 per day in mid-2014 to an average gross cost of $607 per day in mid-2020, which is **61% of the initial gross costs**.
  - The gross cost has decreased primarily due to utilization shifts from Sovaldi and Harvoni® prior to 2017 to less costly Epclusa®, Mavyret®, and the two authorized generics—ledipasvir-sofosbuvir and sofosbuvir-velpatasvir—after 2017.
- The net cost of HCV DAAs as of the second quarter (Q2) of 2020 (measured by WAC less pharmacy discounts, patient assistance, and manufacturer-funded price concessions) has also decreased on average since mid-2014. The average net cost was $201 per day in mid-2020.
  - As additional HCV DAA treatments have become available and increased competition, rebates and other price concessions have further decreased the net cost, which as of mid-2020 had dropped to **22% of the initial net costs**.
- We reviewed various pharmacoeconomic literature, which primarily uses the quality-adjusted life year (QALY) metric to conclude that **DAAs at their 2014 gross cost were cost-effective in the long term**. Treatment costs have decreased since the cost-effectiveness studies were published, indicating improved cost-effectiveness at the lower prices mid-2020, all else equal.
  - The DAAs fall within the commonly used cost-effectiveness threshold ($100,000 or $150,000 per QALY) and Sovaldi was considered cost-effective at $84,000 for the 12-week course that has a high capability of curing HCV.
  - However, the cost-effectiveness analyses do not assess affordability and short-term budget impact, which was a challenge for U.S. payers.

## Background

[1] This range is based on the average net daily cost of an 8 or 12 week DAA regimen across all products. The net daily cost is inclusive of all pharmacy discounts, patient assistance, and manufacturer-runded price concessions across all payer segments, per SSR Health estimates.

## DEFINING THE COST OF HCV TREATMENTS

This report exclusively focuses on the direct prescription drug costs of HCV DAA treatments and the changes over time. Indirect costs, such as changes in medical costs or productivity, or other prescription drug costs, were not included in our analysis. Specific manufacturer price concessions are considered proprietary information, which makes it difficult to understand the costs of HCV treatments. Throughout our report, we provide insight and focus specifically on two different types of costs:

- Gross cost, defined as the wholesale acquisition cost (WAC) in this report, represents the price at which the manufacturer sells to wholesaler and excludes, for example, pharmacy discounts or other price concessions.
- Net cost is defined as the WAC less pharmacy discounts, patient assistance, and manufacturer-funded price concessions, such as rebates, coverage gap discounts in Medicare, federal and supplemental rebates in Medicaid, and 340B drug pricing.

## OVERVIEW OF HEPATITIS C AND HCV TREATMENTS

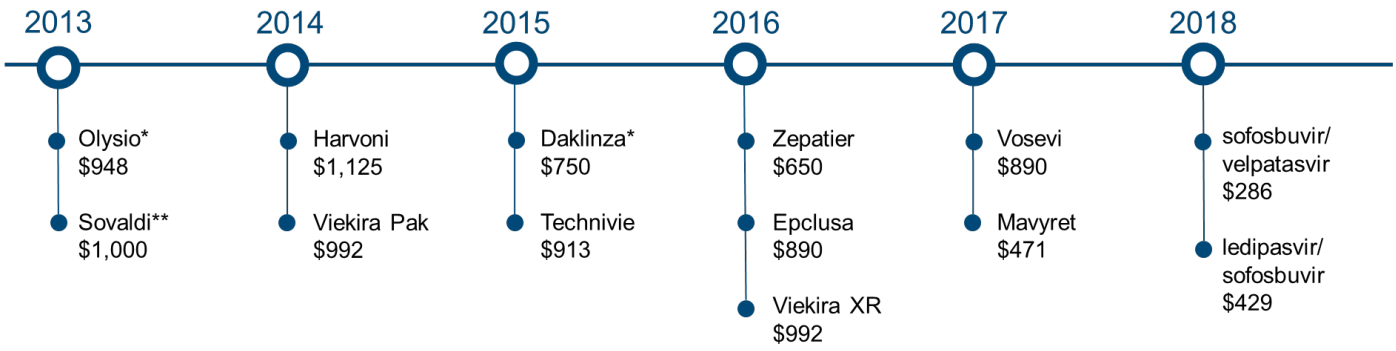
Hepatitis C is a liver infection caused by the hepatitis C virus (HCV) that leads to liver inflammation. HCV is a bloodborne illness that is usually spread through blood or bodily fluids that contain blood. HCV can be spread through sharing needles or syringes, perinatal transmission at birth, healthcare exposures, and other methods that involve coming into contact with blood from an infected individual.[1] Prior to the widespread screening of the blood supply in 1992, HCV was also spread through blood transfusions and organ transplants.

The Centers for Disease Control and Prevention (CDC) reported 137,713 total new cases of chronic hepatitis C in the United States in 2018.[2] Because the disease can be asymptomatic, approximately four in 10 people with hepatitis C do not know they are infected with the disease.[3] In 2020, the CDC updated its recommendations for HCV screening to include one-time screening for all adults, while the U.S. Preventive Services Task Force (USPSTF) recommended screening for adults aged 18 to 79. Both organizations have expanded screening recommendations compared to the prior screening recommendations for adults born between 1945 and 1965.[4,5]

Untreated chronic hepatitis C can result in liver damage, cirrhosis (scarring of the liver), liver failure, and liver cancer. Hepatitis C is a leading cause of death from liver disease in the United States, with 15,713 deaths reported by the CDC in 2018.[6] Patients with untreated HCV have an approximate fivefold increase in all-cause mortality and twentyfold increase in liver-related mortality.[7] For many decades, cirrhosis secondary to HCV infection was the leading cause of liver transplantation.[8] HCV is associated with a substantial economic burden, which includes direct medical costs and indirect costs due to impaired quality of life.[9]

The direct-acting antivirals (DAAs), particularly all-oral regimens, have changed the treatment landscape of HCV. Prior to the availability of DAAs, HCV was primarily treated with interferons and ribavirin-based regimens, which required self-injection, had limited efficacy, and had serious adverse effects (e.g., influenza-like symptoms, depression, neutropenia, anemia). In 2011, first-generation DAAs—Victrelis® and Incivek®—provided slightly improved efficacy, but were limited to treating patients with HCV genotype 1 and still required the use of interferons and ribavirin. In 2013, second-generation DAAs Sovaldi® and Olysio™ were launched; Sovaldi plus ribavirin, Sovaldi plus ribavirin plus peginterferon, and Sovaldi plus Olysio had lower rates of side effects and high cure rates, as defined by sustained virologic response (SVR12), or no detectable amount of HCV after 12 weeks post-treatment.[10] These advances led to practice guideline updates by the American Association for the Study of Liver Diseases (AASLD) and rapid uptake.[11] Since then, interferon-free and ribavirin-free regimens (e.g., Harvoni®, Zepatier®, Epclusa®, Vosevi®, Mavyret®) became available, which further improved treatment options for HCV patients, with continued high cure rates of over 95%.[12] Many therapies expanded indications to all virus strains or genotypes and/or shorter treatment duration, such as eight or 12 weeks of treatment, compared to as much as 48 weeks with first-generation DAAs. Refer to Figure 1 for a timeline of U.S. launch dates for second-generation DAAs and the associated gross cost per day.

**FIGURE 1: HCV DAA TIMELINE OF U.S. LAUNCH AND GROSS COST PER DAY**



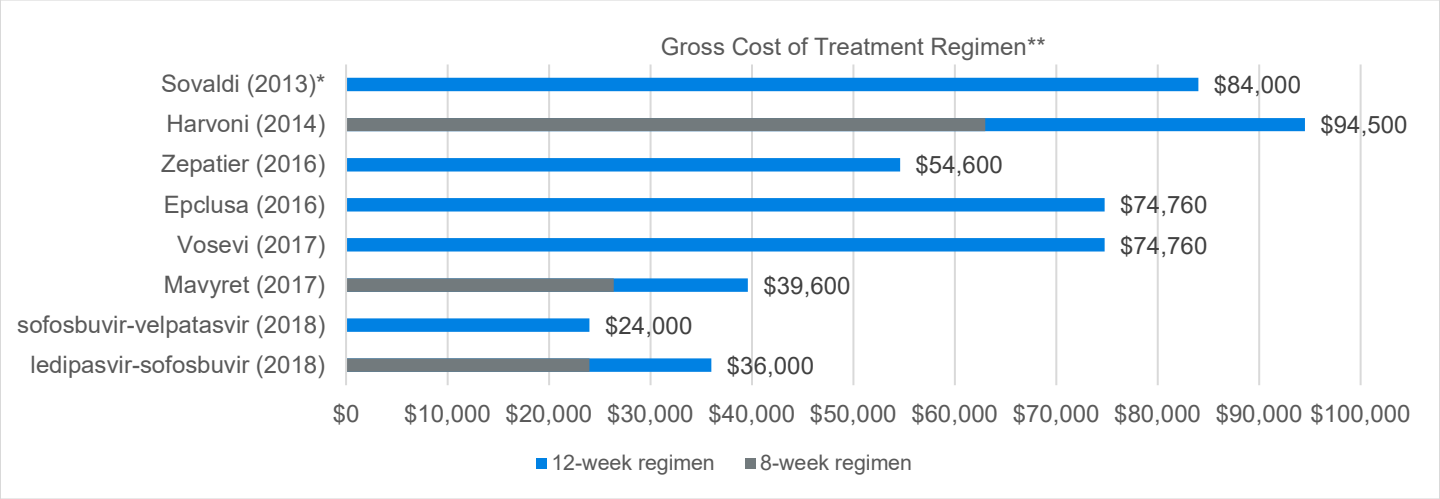
** Therapy was used in combination with Sovaldi. The cost here reflects the cost of the specified therapy alone.*
*** The cost reflects the cost of Sovaldi alone. Sovaldi must be used in combination either with other DAAs (Olysio™ or Daklinza™) or with other agents (ribavirin or ribavirin and peginterferon alfa).*
*Source: Medi-Span Price Rx*

# Results

### CHANGES IN THE GROSS COST OF HCV TREATMENTS

In Figure 2, we provide the gross costs as of each DAA's launch date, for a range of treatment regimens recommended by the AASLD. The gross cost of each individual DAA has remained the same since launch as manufacturers have not increased prices since the launch of the drugs. Note that we focus on the top utilized regimens as other regimens were eventually replaced by other treatments. Figure 2 demonstrates, on average, that the gross expenditure per course of treatment has decreased with more recent launches, due to the combination of lower gross cost and shorter treatment duration options.

**FIGURE 2: GROSS COST OF HCV DAA TREATMENT COURSE, SORTED BY LAUNCH DATE**



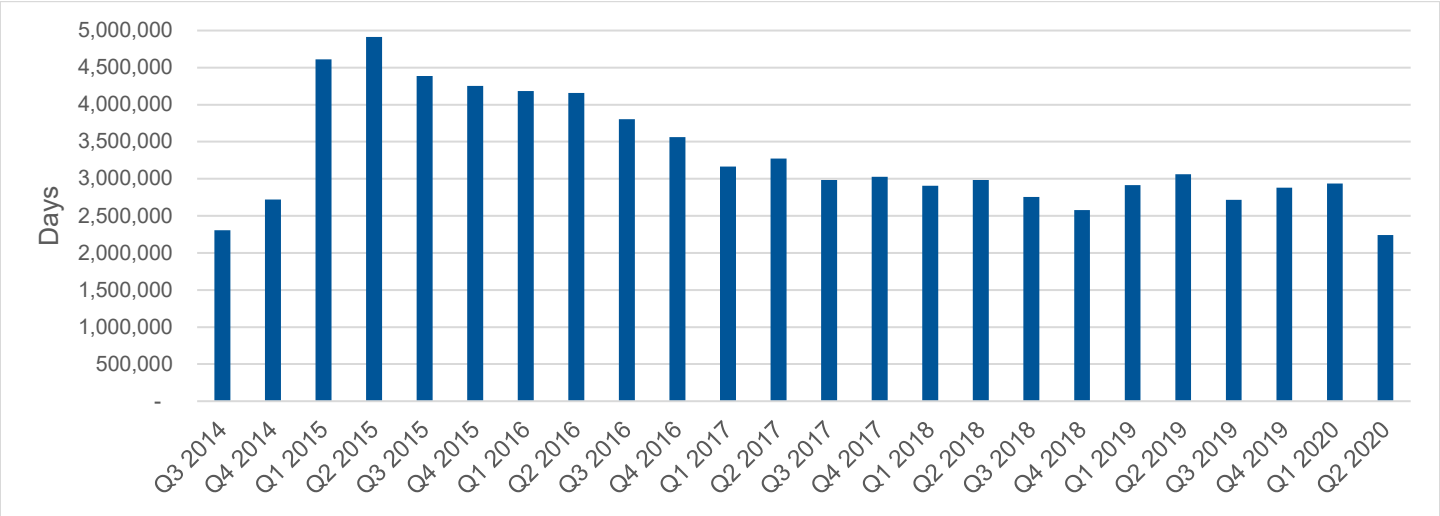

** The cost reflects the cost of Sovaldi alone. Sovaldi must be used in combination either with other DAAs (Olysio or Daklinza) or with other agents (ribavirin or ribavirin and peginterferon alfa).*
*** Other regimens and durations are available based on specific patient characteristics and HCV genotypes.*
*Source: Medi-Span Price Rx*

### CHANGES IN THE AGGREGATE GROSS AND NET COST OF HCV TREATMENTS

In addition to the study of changes in gross price, we also investigated the effects of the combination of: a) shifts in utilization to the newer, lower-priced options, and b) changes in gross price by product. To provide the baseline gross and net spend, utilization, and treatment market share, we summarized prescription claims data for the top utilized HCV DAA regimens in the United States, using IQVIA MIDAS™ data period Q4 2014 to Q2 2020, and calculated total gross expenditure using Medi-Span Price Rx and total net expenditure using data from SSR Health.

Figure 3 highlights two trends. First, these DAA treatments, being largely curative (with more than 95% SVR12) in the real-world, satisfied pent-up demand in the early years (2014 to the peak in Q2 2015).[13] In other words, the utilization increased quickly due to new treatment options for patients who were not cured with other HCV treatments, or were not able to complete those treatment regimens due to severe side effects. Following this time, as more HCV patients were successfully cured, the demand for the DAAs has reduced as progress has been made toward potential elimination.[14] Utilization has largely remained stable since 2017 until Q2 2020, which was the time of the first major wave of COVID-19 in the United States. Second, utilization by number of days has declined over time as shorter treatment regimens became available.

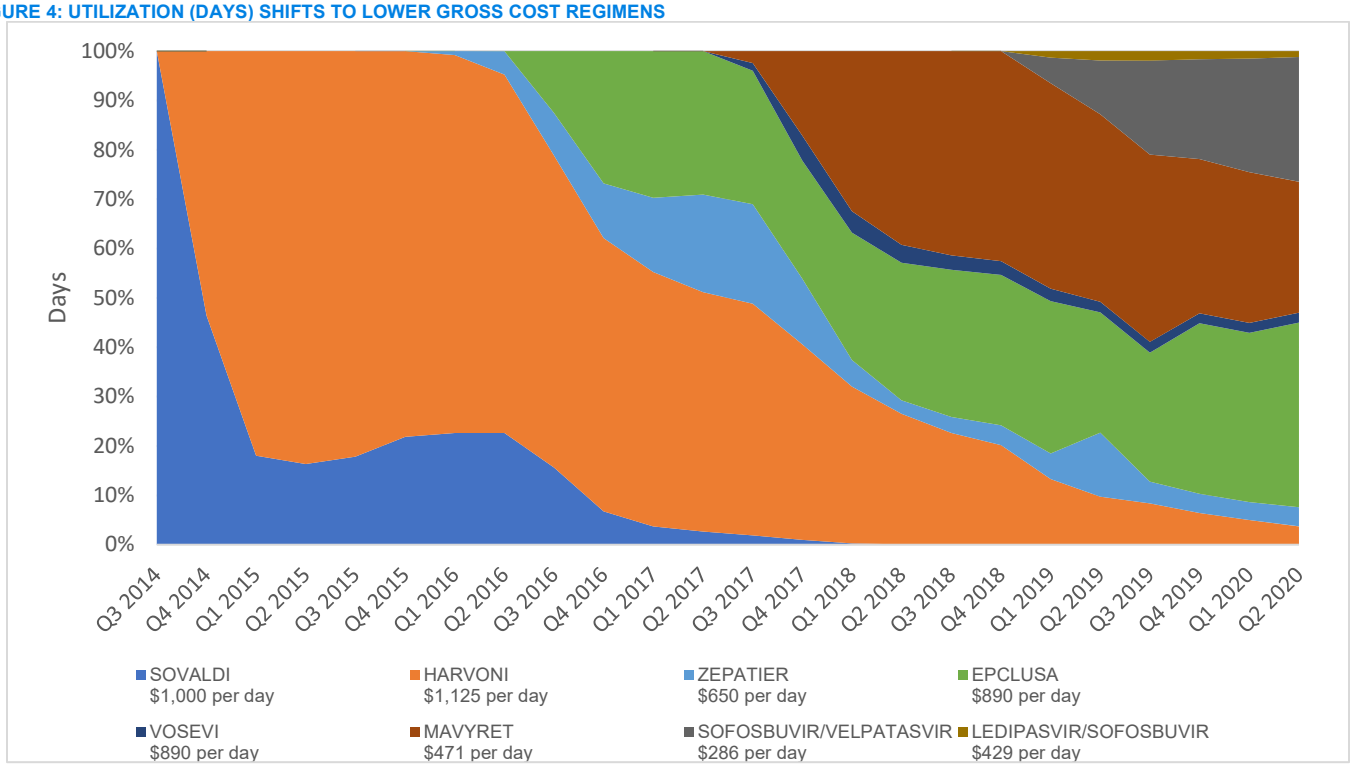
**FIGURE 3: TOTAL HCV DAA UTILIZATION (DAYS)**




*Source: IQVIA MIDAS™ accessed on April 30, 2021*

The remaining impact contributing to a lower gross expenditure on HCV DAAs is attributed to the launch and utilization of treatment options with a lower gross cost in recent years. As shown in Figure 4, the mix primarily consisted of Sovaldi and Harvoni prior to 2017 compared to less expensive Epclusa, Mavyret, ledipasvir-sofosbuvir, and sofosbuvir-velpatasvir after 2017.

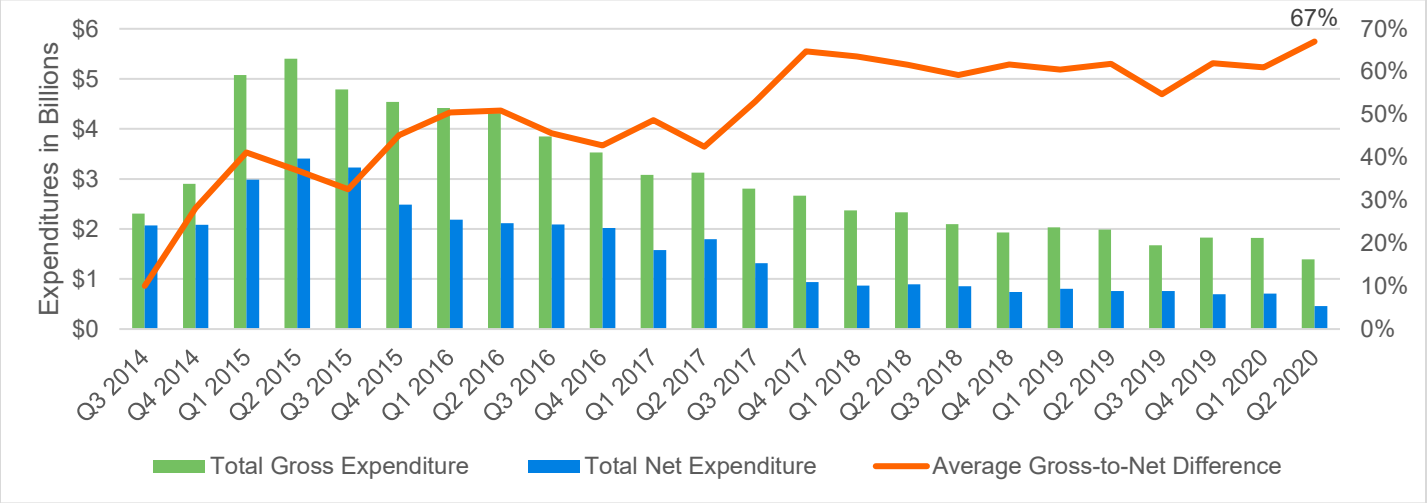
**FIGURE 4: UTILIZATION (DAYS) SHIFTS TO LOWER GROSS COST REGIMENS**




*Source: IQVIA MIDAS™ accessed on April 30, 2021, and Medi-Span Price Rx*

Figure 5 illustrates the total U.S. gross and net spend in the combination of commercial, Medicare, and Medicaid since Q3 2014.

**FIGURE 5: TOTAL HCV DAA GROSS AND NET EXPENDITURE BY QUARTER**

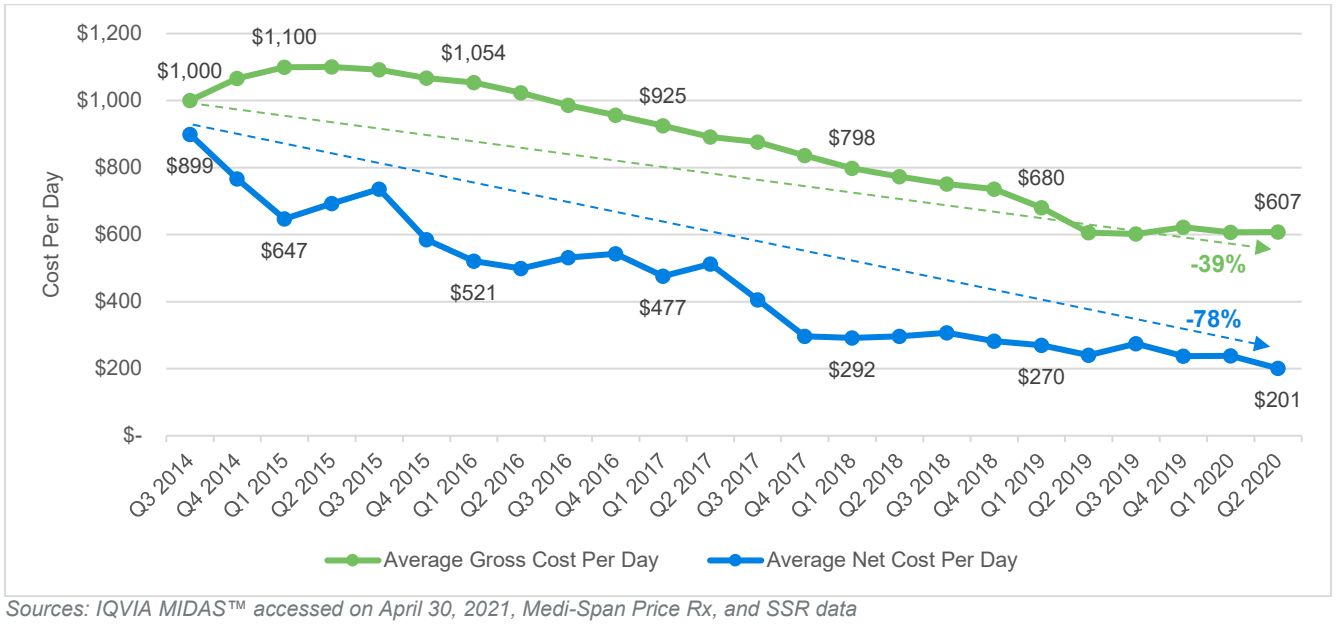



*Sources: IQVIA MIDAS™ accessed on April 30, 2021, Medi-Span Price Rx, and SSR data*

The shift from higher to lower gross cost drugs, combined with an increase in the gross-to-net cost difference (67% average gross to net in Q2 2020), has led to a significant decrease in HCV DAA expenditures as illustrated in Figure 5. The total gross expenditure on prescription drug HCV treatments has decreased by 75% from the peak in Q2 2015 to Q2 2020. The total net expenditure follows similar trends, decreasing by 86% since the peak.

As shown in Figure 6, the cost per day decreased over time due to the introduction and utilization of drugs that have lower gross cost, with additional competition driving down net cost. The average gross cost per day of HCV DAAs in Q2 2020 has decreased by 39% compared to the gross cost per day in Q3 2014. Average net cost in Q2 2020 was a 78% reduction compared to Q3 2014 net cost per day, and this represents 22% of the average gross costs per day in Q3 2014. An average treatment of 8 or 12 weeks would have a net cost of roughly $11,500 to $17,000 per treatment (i.e. $201 per day, 7 days per week, for 8 or 12 weeks).

**FIGURE 6: AVERAGE HCV DAA GROSS AND NET COST PER DAY BY QUARTER**




*Sources: IQVIA MIDAS™ accessed on April 30, 2021, Medi-Span Price Rx, and SSR data*

### VALUE ASSESSMENTS OF HCV DAA TREATMENTS

Despite considerable improvements in efficacy, safety, and tolerability compared to the former standard of care, DAAs immediately generated an intense public debate about the cost, associated value, and affordability of the treatments.[15] Many pharmacoeconomic studies were conducted to assess the long-term cost-effectiveness of DAA therapies. Cost-effectiveness is a comparison of a treatment intervention's cost to its outcomes. Cost-effectiveness is an assessment of cost and health outcomes measured in, for example, quality-adjusted life years (QALYs). In the United States, cost-effectiveness thresholds can vary widely. The Institute for Clinical and Economic Review describes its benchmark for cost-effectiveness as $100,000 to $150,000 per QALY.[16] We reviewed and summarized the literature results regarding cost-effectiveness.

- In 2014, the Institute for Clinical and Economic Review published a final report assessing DAA therapies among the genotype 1 chronic HCV population. Cost-effectiveness models were constructed for Sovaldi, Harvoni, and Olysio and found all three regimens to be cost-effective, relative to interferon plus ribavirin, among a mixed cohort of treatment-naïve and treatment-experienced patients. As an example, Harvoni's cost per QALY was $19,229 and $13,611 under a "treat all" strategy and under a "treat at advanced liver disease stage" strategy, respectively. The cost input was Harvoni's gross cost (WAC) at launch.[17]

- Chhatwal and colleagues developed another payer-perspective model, assessing sofosbuvir-based therapies (Harvoni and Sovaldi) among the chronic HCV population with genotypes 1 through 4. Overall, relative to standards of care at the time (interferon plus ribavirin, with or without Incivek or Victrelis), sofosbuvir-based therapies had a cost per QALY of $55,378. Subsequently, at a benchmark threshold of $100,000 per QALY, the researchers found sofosbuvir-based therapies are cost-effective in most patients. The cost inputs of Harvoni® and Sovaldi® were their respective gross costs (WACs) at launch.[18]

- Notably, most published studies focused on patients across all liver disease severity levels or those with more severe or advanced liver disease. In practice, as more patients with severe liver fibrosis (i.e., METAVIR fibrosis scores F3 and F4) are treated and achieve clinical "cure" (i.e., SVR12), those with less severe liver fibrosis (i.e., METAVIR fibrosis scores F1 and F2) remain in the treatable population, which could impact the applicability of published pharmacoeconomic studies on the remaining treatable population. It is therefore important to evaluate cost-effectiveness in the context of patient population mix.

- Finally, studies focusing on the direct or indirect medical cost offsets related to DAA usage are scarce. Jung et al. (2020) explored this topic in a Medicare population, and found that DAA therapy is associated with a decrease in HCV or liver disease-related medical cost 30 months after treatment. The authors (Jung et al.) accounted for rebates and applied a 22% discount to the list prices.[19]

Generally, the literature supported the cost-effectiveness of the drug over long-term time horizons. Notwithstanding, the financial impact to payers became apparent when healthcare stakeholders attempted to assess the value of DAAs and to budget for potential patient utilization. Many payers were concerned about the HCV patient "warehouse" (patients who held off treatments in anticipation of curative HCV DAAs) and the short-term budget affordability. As a response, some payers imposed strict policies restricting patient access to DAAs. The ICER value framework requires payers to factor in their own short-term budget considerations and understand the impact of drug costs.[20]

## Data, Methodology, and Limitations

### DATA SOURCES

- We used IQVIA MIDAS™ data period Q4 2014 to Q2 2020 accessed on April 30, 2021, to study changes in volume of HCV DAAs within the U.S. markets. IQVIA MIDAS data combines country-level data, healthcare expertise, and therapeutic knowledge and is designed to support analyses of trends, patterns, and similar types of analyses. The MIDAS data contains the top utilized HCV DAA regimens and does not include volume for Olysio, and Technivie™ and Viekira XR™ utilization is combined with Viekira Pak™. The market share of these specific regimens is not anticipated to be significant.

- We relied on estimates of average gross-to-net costs developed by SSR Health LLC as discounts and rebates are highly confidential. SSR Health uses its own methodology to derive information and estimate net prices, which we relied on for this report. SSR Health provides cost information related to the relationship between the average WAC and net cost and utilization patterns on a quarterly basis.

- We relied on pricing information from Medi-Span Price Rx.

- The IQVIA and SSR data was not audited but we reviewed for consistency and reasonability.

### METHODOLOGY

We used IQVIA MIDAS utilization reports of HCV DAAs in the United States from Q4 2014 to Q2 2020 to summarize cost and utilization metrics, adding wholesale acquisition cost information from Medi-Span Price Rx and SSR Health's net cost estimates to produce volume-weighted averages.

## LIMITATIONS

Our analysis and methodology are limited to information available within the data sets. Our analysis is not able to account for the following:

- Costs due to multidrug therapy regimens and consolidation of regimens. Over the years, the American Association for the Study of Liver Diseases (AASLD) guidelines no longer recommend treatment with two separate drugs, such as Sovaldi plus Olysio or Daklinza. Additionally, the World Health Organization guidelines were updated in 2018 to recommend the use of pangenotypic DAA regimens, which could have impacted prescribers' choice of treatment regimen.[21]
- Different components of net price reduction—i.e., separate rebate from discount or other reductions.
- Impacts of price changes on beneficiary cost sharing, state or federal government expenditures, or plan-specific impacts, all of which vary by payer type.
- Other components that are not available in the data set, such as the drug efficacy for patients achieving SVR or patients discontinuing treatment due to adverse events.

This report was prepared for Gilead Sciences, Inc., a life sciences company that manufactures several HCV DAA therapies. Our findings are based on an analysis of U.S. cost and volume across commercial, Medicare, and Medicaid. Contracting terms vary widely among markets and regions. Results from this analysis may not be applicable to other therapeutic areas or markets.

The results presented herein are estimates based on the best information available as of the date of publication. Differences between our results and other analyses may arise due to variations in definitions, methodology, or data updates.

This report represents the opinion of the authors and is not representative of the views of Milliman. Milliman does not endorse any public policy or advocacy position on matters discussed in this report.

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