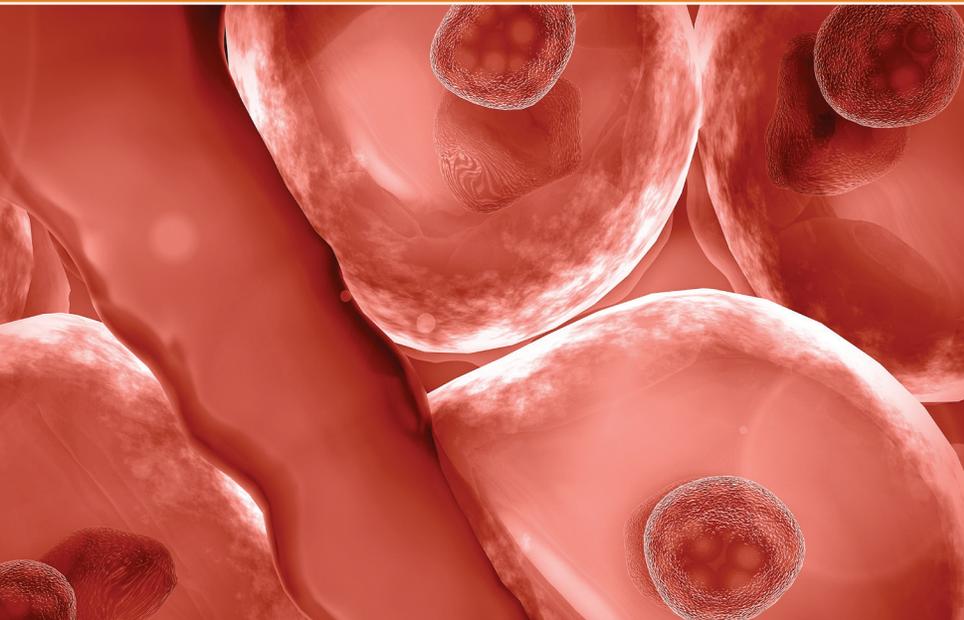


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Twenty-Five Years of Progress Against Hepatitis C: Setbacks and Stepping Stones





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Cover image (top): Computerized image of Hepatitis C (Getty Images)
Cover image (bottom left): Artist rendering of living cells (Getty Images)

Executive Summary

Hepatitis C is a devastating viral disease which progresses slowly over time and causes very serious damage to the liver. The disease is the leading cause of liver cancer and the most common reason for liver transplant.

Tremendous research advances in recent years are transforming treatment of this debilitating disease. Today, more than 90% of patients with the most common form of the disease can expect to be cured in as little as 8 weeks with newly approved antiviral therapies. This stands in stark contrast to cure rates of 41% over 48 weeks with severe side effects for the same patients just over a decade ago.

These successes emerged from many unsuccessful research attempts over the years. Between 1998 and 2014 alone there were 77 investigational medicines that failed in clinical trials. Setbacks in biopharmaceutical research are inevitable but also necessary as stepping stones to help researchers understand effective pathways for targeting and treating disease. These so-called “failures” paved the way for the 12 new medicines approved by the U.S. Food and Drug Administration over the same period which have ushered in a new era of treatment of hepatitis C.

Hepatitis C research successes have built over time. Following the identification of the virus in 1989, stepwise improvements in interferon-based therapy ensued over the next two decades. Simultaneously, researchers were applying lessons learned from successes in the treatment of HIV/AIDS and began exploring similar modes of action against the hepatitis C virus. After years of research and many setbacks, the first of these medicines—called “direct-acting antivirals”—were approved in 2011. Since that time, many more of these medicines have been approved and researchers are finding even greater success in employing a combination of antiviral therapies to more effectively combat the disease.

Today, there are 75 medicines to treat hepatitis C in development in the United States. These medicines promise to improve cure rates further, reduce side effects and duration of treatment, and expand treatment options. The future is truly hopeful for patients with hepatitis C.

“Having hepatitis C virus, as with any invisible chronic illness means that your life as you once knew it is changed. Just because you can’t see those changes doesn’t mean they are not there and felt by us.”

– Hepatitis C Association¹



Introduction

We have seen a revolutionary change in the treatment of hepatitis C virus (HCV). The virus that causes this form of hepatitis was first identified 25 years ago and was viewed as largely incurable.² Since then public health officials have worked to prevent and screen for the disease and researchers have developed effective new treatments. New medicines have resulted in dramatic progress with potential cure rates rising from 6% to 52% to more than 90% today.^{3,4,5}

More new medicines are on the way. Most of this progress has occurred in just the last three years with newer, more effective therapies transforming the trajectory of the disease for many patients. Today, we're looking at a future in which hepatitis C may be considered a rare disease.⁶

What is behind these remarkable advances? The medicines that are now transforming treatment for hepatitis C patients are the result of decades of scientific challenges and setbacks. However, these so-called “failures” reflect the nature of the drug discovery process. Research setbacks are an important part of this process, and they have been integral in laying the foundation for recent successes.

This report examines the human and economic burden of hepatitis C, how treatment has progressed, and the challenges researchers have faced in developing new medicines to fight this chronic disease which affects an estimated 3.2 million people in the United States and 170 million around the world.⁷

The Human and Economic Burden of Hepatitis C

Hepatitis C is a devastating viral disease that generally progresses slowly, meaning patients often remain asymptomatic—and unaware they are infected—until very serious and often expensive complications emerge as a result of damage to the liver. It is estimated that about half of those infected are not aware that they carry the virus.⁸

The hepatitis C virus is blood-borne and was often spread by blood transfusions prior to 1992 when screening measures went into effect. HCV slowly damages the liver over many years, often progressing from inflammation to scarring (fibrosis) to permanent, irreversible scarring (cirrhosis). As liver damage increases, symptoms eventually include jaundice, joint pain, fever, fatigue, nausea, and loss of appetite, among others.

Once a patient has cirrhosis, the liver is unable to heal itself, and this condition can rarely be reversed. Therefore, for those with end-stage liver disease, treatment is more focused on preventing further damage to the liver in an effort to avoid life-threatening complications, including liver cancer, liver transplantation, and premature death. Hepatitis C has also been associated with other co-morbid conditions, including diabetes, kidney disease, and depression.^{9,10,11}

Variations in the genetic material making up the virus result in at least six different forms of the virus called “genotypes.” Knowing what genotype a patient is infected with is important because the genetic material determining each genotype also determines how a patient will respond to various treatments. Genotype 1 is the most common form of the virus and historically has been considered the most difficult to treat. It is estimated that more than 70% of all hepatitis C infections in the United States are genotype 1.^{12,13,14}



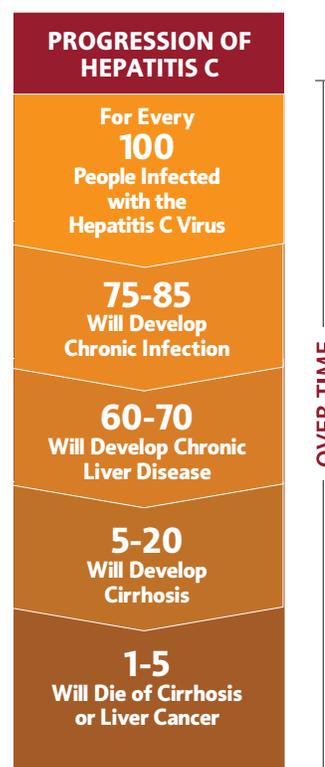
Despite highly effective measures to prevent the transmission of hepatitis C via blood transfusions, the disease remains an epidemic that takes a devastating human toll. Consider that:

- In addition to the **3.2 million** people in the United States chronically infected with hepatitis C, an estimated **17,000** become newly infected annually.¹⁵
- More than **16,000** people in the United States died in 2010 from hepatitis C-related liver disease.¹⁶ Accounting for under diagnosis, new research estimates hepatitis C-related mortality in the United States may be closer to **53,000** deaths annually.¹⁷
- Hepatitis C is the leading cause of cirrhosis and liver cancer, and the number one cause of liver transplants in the United States.¹⁸
- Each year more Americans die from hepatitis C than from human immunodeficiency virus (HIV).¹⁹
- Baby Boomers make up **75%** of hepatitis C cases.²⁰

In the absence of recently approved therapies to effectively treat the disease, it has been estimated that the prevalence of compensated cirrhosis (liver scarring that produces few or no symptoms) in the United States would have peaked in 2015 at 626,500 cases; decompensated cirrhosis (severe liver scarring that disrupts bodily functions) would have peaked in 2019 with 107,400 cases; and HCV-caused liver cancer would have peaked in 2018 at 23,800 cases. The same study projected that in the absence of newly available therapies, mortality among HCV patients would have peaked in 2020 with 69,440 deaths, of which 29,650 would be attributable to liver disease caused by HCV.²¹

The impact of hepatitis C can also be measured in terms of the significant financial burdens placed on the U.S. health care system as a result of the disease. Not only are current direct health care costs significant per patient (see Table 1), but the total projected costs associated with the disease and its very serious complications are anticipated to grow in coming years in the absence of effective treatment options.

The scientific advances made in recent years by biopharmaceutical researchers as they combat the hepatitis C virus have already begun to have a tangible impact on thousands of patients. As more sufferers of hepatitis C gain access to next generation treatments, the transformative impact of these medicines on society at large will continue to grow.



Source: Centers for Disease Control and Prevention. "Hepatitis C: General Information Fact Sheet." Atlanta, GA: CDC. <http://www.cdc.gov/hepatitis/HCV/PDFs/HepCGeneralFactSheet.pdf>

Table 1.

HEPATITIS C RELATED COSTS	
\$24,000	Average annual cost per patient with hepatitis C
\$60,000	Average annual cost per patient with end-stage liver disease
\$112,000	Average annual cost per patient with liver cancer ²²
\$500,000	Approximate cost per patient requiring a liver transplant ²³

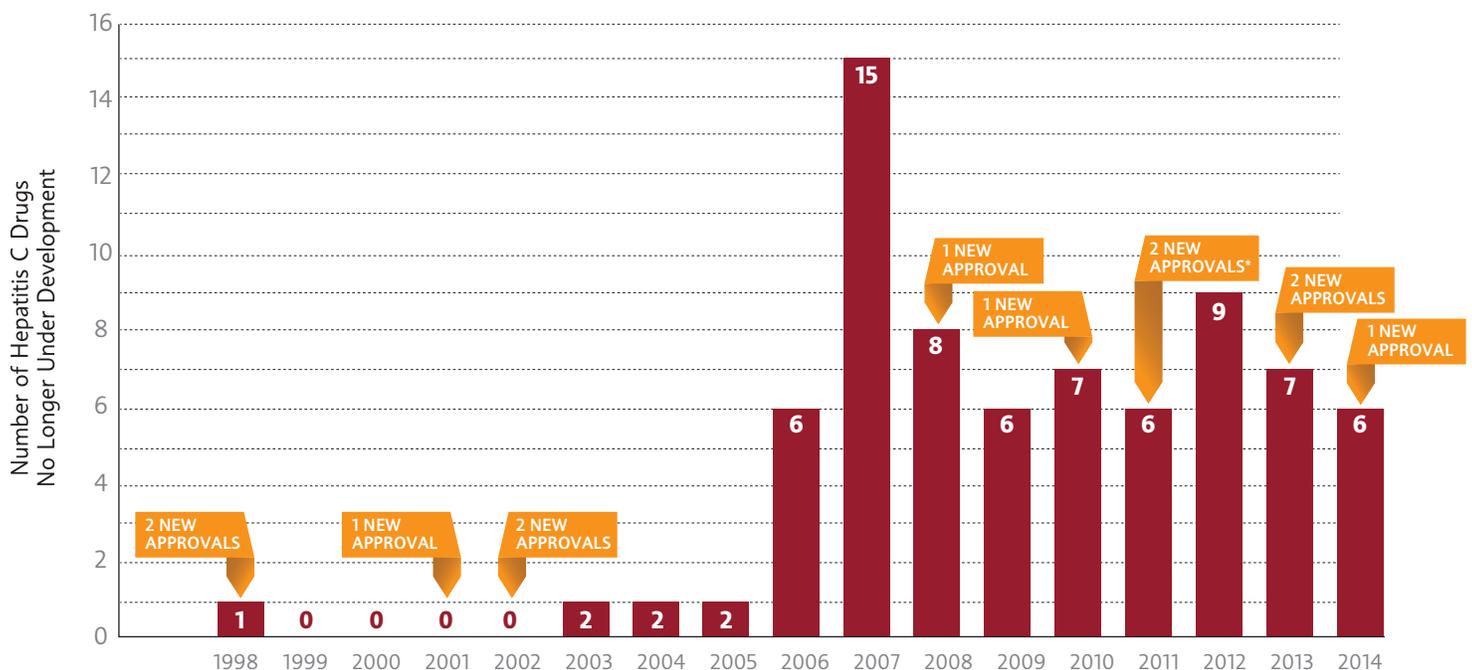
Research Setbacks and Stepping Stones in Hepatitis C

Recent and forthcoming approvals of treatments for hepatitis C are clearly game changing for patients and the health care system. But how did we get to these successes? Like most biopharmaceutical innovation, these advances have emerged from many setbacks and have built on one another over time. For years, the development of new drugs to treat hepatitis C was marked by a daunting number of unsuccessful attempts.

Between 1998 and 2014 there were **77 investigational medicines that failed** in clinical trials. These include projects that were discontinued, suspended, or had no development reported. (For more details see Methodology section on page 14.) These unsuccessful projects laid the groundwork for the **12 new medicines** approved by the U.S. Food and Drug Administration (FDA) over the same period. (See Unsuccessful Hepatitis C Drugs in Development, 1998-2014.)

These so-called failures are actually central to the process of biopharmaceutical progress. Researchers use the knowledge gained from these studies to inform new attempts. Despite many setbacks, hepatitis C researchers continued their work and eventually succeeded in developing recent treatment advances. It is a result of this long iterative process that we have seen a transformation in hepatitis C treatment in recent years.

UNSUCCESSFUL HEPATITIS C DRUGS IN DEVELOPMENT
1998-2014



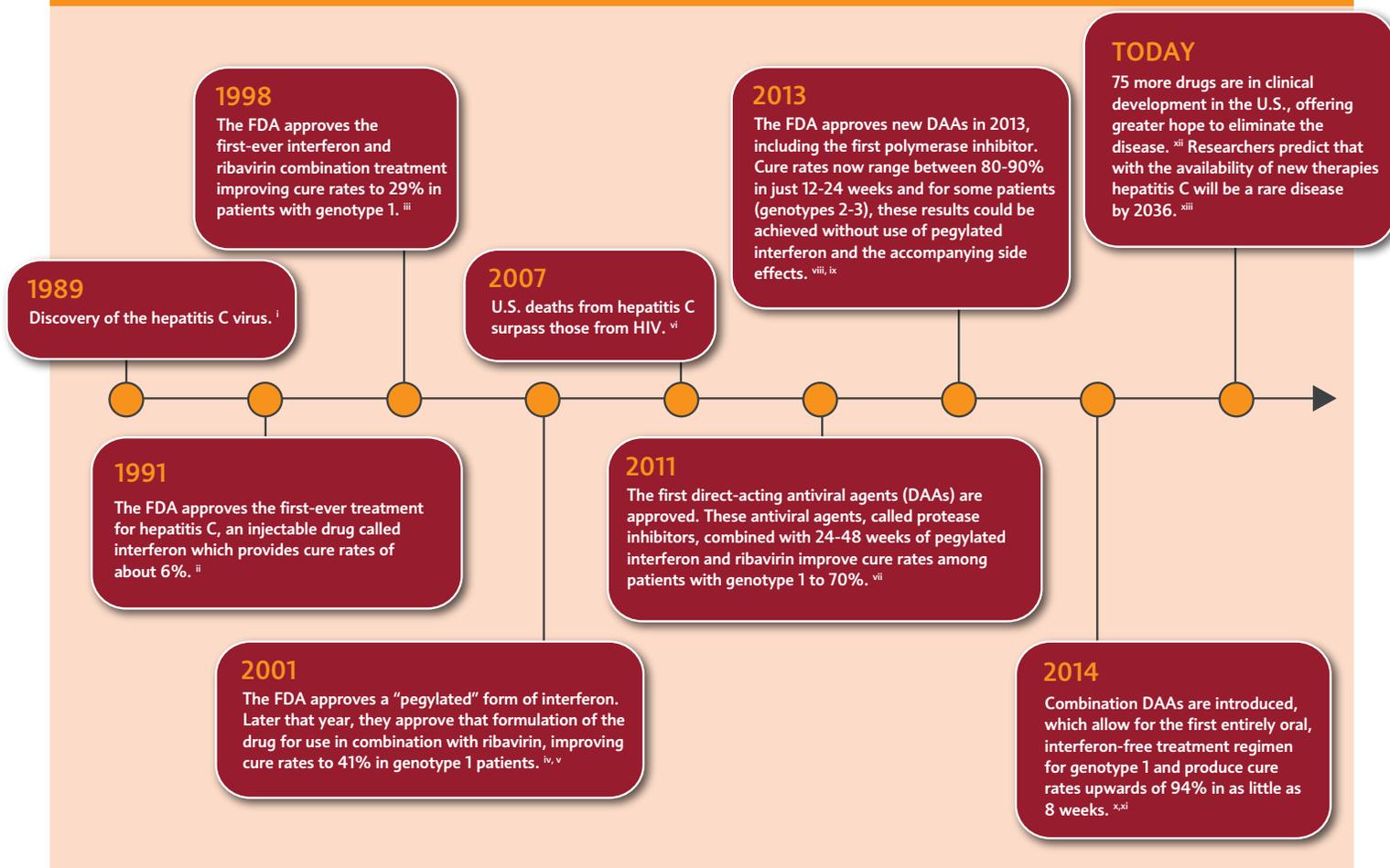
77 TOTAL UNSUCCESSFUL DRUGS | 12 TOTAL APPROVED MEDICINES

*One product was later withdrawn from the market.
Source: PhRMA analysis of Adis R&D Insight Database, 2 December 2014.

Nature of Scientific and Treatment Progress

The recent remarkable advances in treating hepatitis C built on incremental improvements achieved over the previous two decades to transform hepatitis C from a chronic, fatal disease, to an infection that with new and forthcoming treatments, can be potentially cured.

From Discovery to Cure in 25 Years



Identification and Early Treatment of Hepatitis C

Hepatitis C was first identified by scientists in 1989. Prior to discovery, the virus had simply been known as non-A and non-B hepatitis. Isolating the virus precipitated research into vaccines and exploration of potential therapeutic agents. However, the genetic diversity of hepatitis C and the relatively weak immune response elicited by the infection posed formidable challenges in developing a vaccine.²⁴

Since then, researchers have focused on developing new medicines that combat the infection by producing a sustained viral response (SVR) in patients. Achieving a SVR means there is no evidence of the hepatitis C virus in the patient's blood following the completion of treatment, essentially indicating the patient is cured.

The first medicine to treat hepatitis C was interferon, an injected immunotherapy that helps the body distinguish between infected and non-infected cells, targeting infected cells for destruction. Interferon alpha-2b was approved by the FDA in 1991. Unfortunately, few patients receiving treatment achieved a sustained viral response, with only a demonstrated cure rate of about 6% accompanied by debilitating side effects over an extremely long course of treatment.²⁵

Researchers later discovered the benefits of an antiviral medication called ribavirin. Ribavirin was found to augment the effect of interferon by preventing relapse after the end of

treatment.²⁶ In 1998, the FDA approved the combination of interferon and ribavirin for use in hepatitis C patients, bringing cure rates to 29% for genotype 1 patients.²⁷

In 2001, pegylated interferon, a chemically modified version of interferon designed to persist longer in the patient's body was approved. Later that year, the FDA also approved the pegylated form in combination with ribavirin. A course of weekly interferon injections and twice daily ribavirin pills taken over

48 weeks produced cure rates of 41% for genotype 1 patients and 52% across genotypes.²⁸ Unfortunately, genotype 1 remained more difficult to treat with interferon-based therapy relative to other genotypes, representing a significant unmet medical need for patients with the most common form of hepatitis C.

Yet, for those who responded to interferon-based therapy, these treatments offered an alternative to a future of declining health, potential liver transplantation, or even premature death and represented an important clinical milestone in the treatment of hepatitis C. But these early treatments came with severe side effects for patients, including depression, nausea, anemia, and debilitating flu-like symptoms.²⁹ Many patients discontinued treatment due to the side effects and there were no alternatives to treat patients who were unresponsive to the standard of care.





Achieving a Transformation Step by Step

Recent scientific advances have led to a new era of treatments for hepatitis C. New and forthcoming medicines, known as direct-acting antiviral (DAA) agents, are taken orally and target HCV at each step of the virus's lifecycle. Today, more than 90% of patients with the most common type of the disease taking these medicines can expect to be cured in as few as 8 weeks, and with far fewer side effects.³⁰

The recent successes with DAAs are thanks in part to lessons learned from the development of treatments targeting HIV.³¹ During the mid-1990s and into the 2000s, protease inhibitors had become a major component of combination therapies combating HIV/AIDS. Following the success of therapies targeting HIV, researchers began to explore protease inhibitors to target the hepatitis C virus. This class of medicines works by preventing the virus from binding to the site that the virus's protease enzymes use to replicate.³²

But the development of protease inhibitors for HCV was not easy. In 2003, the first protease inhibitor entered clinical trials for hepatitis C and demonstrated proof-of-principle for this class of medicines in reducing viral load. Unfortunately, clinical development of this particular compound was eventually halted due to safety concerns.³³ Nonetheless, this discovery represented an important step in understanding effective targets for antiviral intervention for hepatitis C.

Issues with side effects continued to challenge antiviral drug development for hepatitis C.^{34,35} During this same period, another class of medicines called polymerase inhibitors began demonstrating promise in clinical trials. Polymerase inhibitors are designed to prevent the virus from replicating by blocking the RNA polymerase enzyme. The first nucleoside polymerase inhibitor entered clinical trials in 2004. However, due to concerns over gastrointestinal side

HIV Versus Hepatitis C

Hepatitis C research built on the successes of HIV treatment, but there are important differences between these two viruses.

HIV	HEPATITIS C
HIV is a retrovirus that integrates into the host DNA and causes persistent infection.	HCV does not integrate host DNA.
HIV therapy can only suppress viral replication below detectability.	Viral clearance, or sustained virologic response (a cure), can be achieved.

Table 2.

NEW GENERATION TREATMENTS FOR HEPATITIS C						
TYPE	YEAR APPROVED	DRUG NAME	GENOTYPE	TAKEN IN COMBO WITH PEG-INTERFERON	TREATMENT DURATION	CURE RATES
Protease Inhibitors	2011	Telaprevir	1	✓	24-48 weeks	63-80% ^{a,b}
	2011	Boceprevir				
	2013	Simeprevir				
Polymerase Inhibitors	2013	Sofosbuvir	1	✓	12 weeks	90% ^c
			2		12 weeks	
			3		12 weeks	
			4		24 weeks	
Combination Therapies	2014	Sofosbuvir	1		12-24 weeks	96% ^d
		Simeprevir				
		Sofosbuvir	1		8-12 weeks	94-96% ^e
		Ledipasvir				

effects, this compound was also discontinued in 2007. In the years that followed, many additional polymerase inhibitors were halted due to concerns over side effects.^{36,37}

Researchers were also discovering another challenge in developing effective treatments against hepatitis C—a challenge reminiscent of earlier difficulties in the development of medicines to combat HIV. Variations in the genetic material making up the hepatitis C virus determine how some patients respond to available antiviral therapies. As researchers explored new drug candidates for the disease, they learned certain mutations of the virus were less likely to respond to different protease and polymerase inhibitors under investigation. By 2007, researchers had already discovered 18 resistant mutations associated with the various protease and polymerase drug candidates in development. Although presenting a challenge initially, these findings enabled researchers to learn, as was the case with HIV, that in order to combat viral resistance in hepatitis C, multiple antiviral therapies targeting different mechanisms of action were necessary. Combination therapies had become the future of DAA treatment for hepatitis C.³⁸

In 2007, the number of unsuccessful drug candidates had peaked, but a number of other novel DAA investigational medicines targeting different aspects of the hepatitis C viral lifecycle were beginning to show promise in the pipeline. After many years of research, the first two DAA medicines, telaprevir and boceprevir, were approved in 2011 to treat patients with genotype 1. Taken in combination with pegylated interferon and ribavirin, this treatment regimen raised cure rates to approximately 70%, with a treatment duration range of 24 to 48 weeks.³⁹

As the first major advance in the treatment of hepatitis C in over 10 years, protease inhibitors provided a much-needed option for patients who failed to respond to previous treatments. However, taken orally in combination with interferon and ribavirin, treatment regimens were complex and severe side effects remained.

Two new oral DAAs were subsequently approved in 2013. Simeprevir was approved for use in combination with pegylated interferon and ribavirin to treat genotype 1 HCV. Simeprevir, also a protease inhibitor, is a once-a-day oral treatment combined with ribavirin and interferon for a course of up to 24 weeks. In clinical trials, simeprevir boosted cure rates to approximately 80 percent.⁴⁰

Shortly thereafter, FDA approved sofosbuvir, the first polymerase inhibitor to treat four different genotypes of HCV. Sofosbuvir was approved for use in combination with ribavirin and a weekly injection of pegylated interferon for genotypes 1 and 4. Importantly, in these patients, the sofosbuvir treatment regimen produced an overall cure rate of 90% in as little as 12 weeks with greatly reduced side effects.⁴¹ Sofosbuvir was also approved to be taken without use of interferon for patients with genotypes 2 and 3—making it the first interferon-free treatment regimen for hepatitis C.

As the search for cures continued, the rapid evolution of hepatitis C treatments took another significant step in 2014 with FDA approval of two new regimens. In October 2014, approval was granted for a fixed-dose pill that combines sofosbuvir with ledipasvir, a nonstructural protein 5A (NS5A) inhibitor. This treatment avoids the use of inteferon and the resulting side effects while also producing cure rates of 94% in as little as 8 weeks. Most recently, FDA followed in November 2014 with the approval of the combination use of simeprevir and sofosbuvir as a second all-oral, interferon- and ribavirin-free treatment option. In clinical trials, this new treatment has shown to achieve an overall SVR of 96% in 12 weeks.^{42,43} Additional new medicines are also in review and are likely to offer new options to patients soon.

“The massive global push to study HIV and AIDS led not only to treatments for that ailment, but to progress in developing drugs for other diseases, such as Hepatitis C.”

– Anthony S. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases⁴⁴





Looking Ahead to New Cures

As breathtaking as recent progress has been, new drugs in development are poised to improve treatment further. A total of **75 medicines** are currently in clinical development in the United States. They include the next generation protease inhibitors, nucleotide analog polymerase inhibitors, and combination or “cocktail” therapies that harness the power of multiple mechanisms of action, as well as new vaccines.⁴⁵

While historically a challenging form of the disease to treat, genotype 1 has been found to respond particularly well to DAA therapies in recent years. Now researchers are increasingly focused on improving cure rates across genotypes, including genotype 3, which has now become the most difficult form of the disease to treat. These potential treatments are projected to provide expanded treatment options for patients, even greater cure rates, shorter treatment durations, and a future without hepatitis C virus.

A note on methodology:

Data are drawn from the Adis R&D Insight database which compiles publicly available information on medicines in development. Projects were counted as “failures” and included in the analysis if they were categorized in the database as “suspended,” “discontinued,” or “no development reported” for the indication “Hepatitis C.” Only projects in clinical development or Food and Drug Administration review were included. In cases where more than one delivery mechanism was tested or where the history included more than one category (e.g., “no development reported” in 2006 and “suspended” in 2007) the latest date included was counted. Diagnostic imaging agents were excluded.

Adis’ Definitions:

- **Suspended:** “This term is used when a company has suspended development of a drug, often in order to focus on the development of some other drug. Development has not been discontinued.”
- **Discontinued:** “The company has chosen to stop development.”
- **No development reported:** “If there has been no activity associated with a drug (no commercial information released, no recently published studies) for 18 months to 2 years, the term ‘no development reported’ is assigned. The time frame depends on the last phase of the drug. This is the term used until a drug is confirmed as discontinued, withdrawn or suspended, or activity is resumed.”

According to correspondence with Adis R&D Insight database editors regarding “inactive” projects, although exact percentages are not available, only a very small proportion of projects categorized as “no development reported” are reactivated and the majority go on to be “discontinued” after more time has elapsed. “No development reported” status is used when development goes silent and the editors see that no activity appears to be happening. They use the term “suspended” when a company states that it is suspending development for any reason. It is quite difficult to determine what percentage of these programs are reactivated because it depends whether another company picks up a license to develop it or whether the company itself will reactivate development at another stage. Generally when a company suspends development a very small percentage of drug programs are reactivated by the same company. A small percentage of suspended projects are out-licensed at which point the chances of reactivation become much higher. There is a very small percentage of discontinued programs that are reactivated.

Approvals are also drawn from Adis R&D Insight database and were cross referenced with “Drugs @ FDA” database.

The analysis goes back to 1998 as the Adis data is less comprehensive before this time. Data are current as of December 2, 2014.

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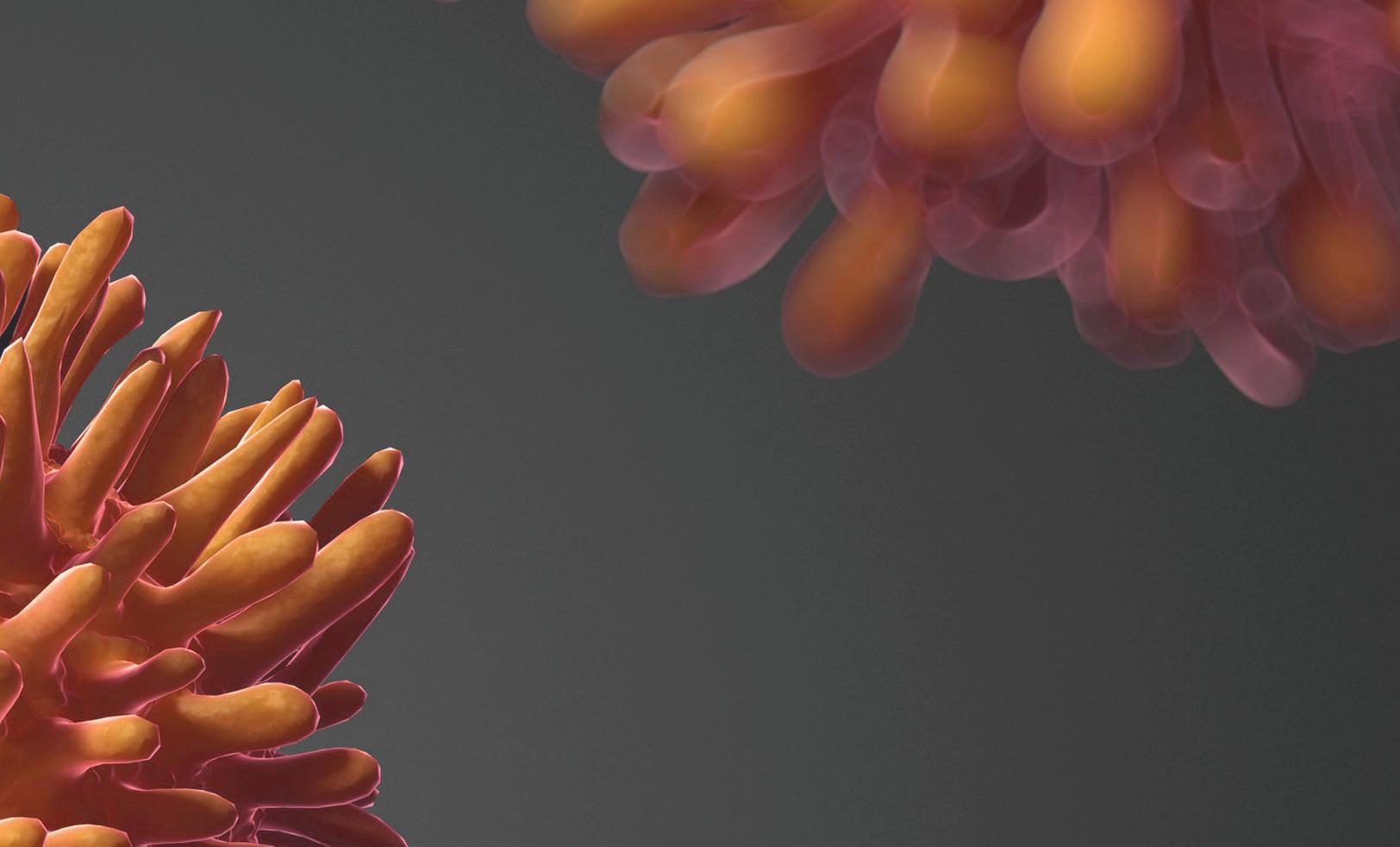
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