# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Reflecting on a Decade of Sofosbuvir Use for Hepatitis C Virus Treatment

Ira M. Jacobson, MD
Professor of Medicine
Director of Hepatology Research
NYU Langone Health
New York, New York

**G&H** Sofosbuvir was approved with ribavirin or pegylated interferon plus ribavirin just over 10 years ago for the treatment of hepatitis C virus infection. Thinking back over the past decade of its use, why was sofosbuvir studied in this area in the first place?

**IJ** Sofosbuvir is a nucleotide analog inhibitor of hepatitis C virus (HCV) NS5B polymerase. The drug mimics one of the normal building blocks of genetic material and is taken up by the polymerase, which is an enzyme. This interferes with the enzyme's ability to take up the normal nucleotide in that position, which must occur for new viral genomes to be synthesized during the replication process. This class of medication had long been used for HIV and hepatitis B virus. Studies showed that the drug was highly potent in laboratory systems used to study viral replication, and it had the additional vital feature of a high resistance barrier. Other nucleotide polymerase inhibitors had been studied previously but conferred lesser degrees of viral suppression. The story of sofosbuvir is incomplete without reference to Dr Michael Sofia, the scientist after whom the drug was named, who was instrumental in developing the drug and received a Lasker Award for his achievements in 2016 along with Drs Charles Rice and Ralf Bartenschlager.

**G&H** Could you summarize the key data that first led to the approval of sofosbuvir approximately 10 years ago?

**IJ** Key data came from the historically important multiarm ELECTRON trial published in *The New England Journal of Medicine* in 2013 by Dr Edward Gane and colleagues. Dr Gane has been a prolific investigator from New Zealand and thought leader in the hepatitis field for many years. In 2011, he had presented data demonstrating sustained virologic response (SVR) in 10 of 10 patients with HCV genotype 2 or 3 treated with sofosbuvir and ribavirin to several overflow rooms at the American Association for the Study of Liver Diseases (AASLD) meeting where one could hear a pin drop. (I recall having been unhappily relegated to a peripheral room, despite my timely arrival, and being obliged to watch the proceedings on a screen, a reflection of the eagerness of many to witness the historic proof of concept of the curability of HCV infection without interferon.) Sofosbuvir alone cured "only" 60%. This study was published in *The New England Journal of Medicine* in 2013, as was another by Dr Eric Lawitz and colleagues showing a 90% SVR rate in more than 300 genotype 1 patients treated with peginterferon, ribavirin, and sofosbuvir for an unprecedented short duration of 12 weeks. This regimen became available to clinicians but was soon supplanted by interferon-free therapy. Had interferon-free therapy with combinations of sofosbuvir and other antiviral drugs not been developed, 12 weeks of pegylated interferon, ribavirin, and sofosbuvir would have been a huge advance in the field because of the brevity of the regimen and the remarkably high response rates compared with interferon and ribavirin alone in genotype 1 patients. These plus additional data led to approval by the US Food and Drug Administration (FDA) of sofosbuvir just over 10 years ago.

**G&H** How did sofosbuvir change HCV treatment when it was first approved?

**IJ** It was revolutionary because it yielded extremely high rates of virologic cure without viral resistance when combined with interferon, and even higher rates of cure (approaching 99%) when combined with the NS5A inhibitor ledipasvir (Harvoni, Gilead), which was approved in 2014 for patients with genotype 1, the dominant genotype in the United States, and genotype 4. Together with other antiviral regimens introduced during this period, a quantum leap was witnessed in this field of medicine. Instead of making incrementally better improvements at frequent intervals, treatment of HCV leapfrogged to near-universal cure rates in one fell swoop. The "coup de grace" was the development of the pangenotypic regimens sofosbuvir/velpatasvir (Epclusa, Gilead) and glecaprevir/pibrentasvir (Mavyret, AbbVie), which were approved by the FDA in 2016 and 2017, respectively. These are the 2 regimens in almost exclusive use today.

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**G&H** Could you discuss research on these sofosbuvir combinations?

**IJ** In early studies, sofosbuvir alone was capable of curing a certain percentage of patients with HCV infection, but not a high enough number, especially in genotype 1 patients, to be sufficient as a stand-alone therapy. In the previously mentioned ELECTRON study, the combination of sofosbuvir and ribavirin was superior to sofosbuvir alone, and when peginterferon was added to sofosbuvir and ribavirin in genotype 1 patients, the results were even better. When protease or NS5A inhibitors were added to sofosbuvir, it became clear that interferon was unnecessary and that unparalleled rates of SVR, in the 95% to 99% range, could be attained with these combinations. The ION-1 and ION-2 studies, both published in *The New England Journal of Medicine*, were conducted in treatment-naive and treatment-experienced patients, respectively, and showed very high rates (again exceeding 95%) of SVR in patients treated with ledipasvir and sofosbuvir. Later trials with the NS5A inhibitor velpatasvir established similar results, this time across all genotypes given the pangenotypic properties of both agents in the regimen.

**G&H** What other research has been conducted on sofosbuvir combination therapy specifically in treatment-experienced patients?

**IJ** There has been extensive research in treatment-experienced patients. All of the early direct-acting antiviral (DAA) regimens were studied in prior interferon nonresponders, as well as in treatment-naive patients, because of the large pool of prior interferon nonresponders in the HCV population. It must be remembered that interferon, initially without and then with ribavirin, was all that was available for 2 decades, and the majority of patients failed therapy because of the dominance of genotype 1 in the United States, suffering significant side effects in the process. In the ELECTRON study, which had many arms studying sofosbuvir, interferon nonresponse predisposed to much lower rates of success with sofosbuvir and ribavirin. However, later studies with DAA combination regimens closed and essentially eliminated the gap eventually between interferon-experienced and -naive patients.

**G&H** How safe has sofosbuvir been shown to be over the years since its approval, particularly in patients with chronic kidney disease, those coinfected with HIV, or those who are transplant recipients?

**IJ** Sofosbuvir is safe and well tolerated in all HCV-infected populations. It is associated with virtually no serious adverse events. Studies have shown occasional systemic symptoms such as headache and fatigue, which were rarely treatment-limiting. For years, sofosbuvir was not recommended in patients with chronic kidney disease because of high serum levels of its major metabolite, but clinical studies eventually showed no incremental side effects and the drug garnered regulatory approval in the United States in 2019 for patients with renal failure, including those on dialysis, using standard dosing.

Sofosbuvir-based regimens have similar efficacy and safety profiles in HIV-HCV patients compared with patients with HCV monoinfection. The pangenotypic regimen of sofosbuvir/velpatasvir in widespread use today is compatible with most antiretroviral drugs, but not with efavirenz, etravirine, or nevirapine. Readily available references such as HCVGuidelines.org (latest version December 2023) or the actual package inserts may be consulted before initiating HCV therapy in HIV-coinfected patients, whether with sofosbuvir/velpatasvir or the other widely used antiviral regimen of glecaprevir/pibrentasvir.

Finally, sofosbuvir is safe in organ transplant recipients. It has high efficacy in combination with an NS5A inhibitor, is safe, and has few drug-drug interactions. The current pangenotypic regimen of sofosbuvir/velpatasvir is well tolerated and highly effective in the posttransplant setting whether the patient has recurrent HCV infection posttransplant or is newly infected via transplantation of an organ graft from an HCV-viremic donor, and may be used safely with current standard immunosuppression protocols.

**G&H** Can sofosbuvir combinations be used in pregnant patients and in children?

**IJ** The potential use of antiviral therapy during pregnancy to prevent the low but real risk of maternal to infant transmission has been of considerable interest. Several case series of relatively small numbers of patients have suggested that treatment with sofosbuvir-containing regimens is safe and effective in both mothers and infants. However, there is no regulatory approval for this indication. As of December 2023, the HCV guidance published by the AASLD and Infectious Diseases Society of America posted online at https://www.hcvguidelines.org/unique-populations/pregnancy suggests that although treatment during pregnancy is not recommended, it can be considered on a case-by-case basis after discussion between the patient and physician regarding the possible risks and benefits.

Sofosbuvir is also safe and highly effective in children. As in adults, it must be combined with another antiviral drug, and it is given at doses adjusted for age. The combination of the pangenotypic regimen of sofosbuvir/velpatasvir was approved by the FDA in 2020 for children aged 6 to 17 years and in 2021 for children aged 3 to 5 years.

**G&H** Currently, when should sofosbuvir/velpatasvir be used and when should other HCV treatments such as glecaprevir/pibrentasvir or elbasvir/grazoprevir be used?

**IJ** All 3 regimens have extraordinary efficacy and safety profiles. However, elbasvir and grazoprevir (Zepatier, Merck), an NS5A and protease inhibitor, respectively, are indicated only for genotypes 1 and 4, and NS5A resistance testing is recommended for patients with genotype 1a. Glecaprevir/pibrentasvir, a pangenotypic combination of a protease and NS5A inhibitor, respectively, confers similar near-universal rates of cure as sofosbuvir/velpatasvir and is effective across the same broad spectrum of patient populations. In some patient populations, which include but are not limited to HIV coinfection or post-transplantation, there may be differences between the 2 combinations in terms of drug-drug interactions, and clinicians should familiarize themselves with these by consulting readily available references.

**G&H** How has pricing of sofosbuvir changed over the years?

**IJ** Pricing came under scrutiny in the public domain after the drug was first approved, but the pricing of HCV regimens has declined significantly since then.

**G&H** What lessons have been learned over the 10 years since sofosbuvir's approval?

**IJ** We continued to learn vital lessons in certain patient populations well after the initial approval of DAA drugs. The most dramatic by far was the hitherto unimaginable scenario of transplanting HCV-positive organs into HCV-negative recipients, almost inevitably resulting in HCV infection that could then be eradicated with near-100% confidence by antiviral therapy after transplantation. This has saved many lives by allowing earlier access to organs. This paradigm has been made possible by collaborations among hepatologists, surgeons, ethicists, health care administrators, institutional review boards, insurers, and legal experts, among others.

The durability of virologic clearance has also stood over time. Patients with negative polymerase chain reaction (PCR) results for HCV RNA 12 weeks after the end of treatment almost never relapse, with rates of such late relapse in the range of 0.1% or less. Some clinicians are content with a 12-week posttreatment PCR, whereas others (such as myself) check once more at the 1-year mark. I cannot, however, recall a personal case in which such late relapse occurred in the era of DAA therapy.

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We have learned that HCV cure stops the progression of fibrotic liver disease (although patients who have

decompensated cirrhosis may still need transplantation). HCV cure also reduces the risk of hepatocellular carcinoma (HCC) by 70% to 80% in compensated cirrhotic patients. However, every active clinician in this area has seen patients who develop HCC even years after HCV cure. Patients with antecedent cirrhosis (F4) are at ongoing risk of HCC and require HCC surveillance with imaging with or without alpha-fetoprotein every 6 months indefinitely. Some experts and guidelines recommend ongoing surveillance in patients with antecedent bridging fibrosis (F3) as well.

A major lesson from HCV therapy, both with interferon and now resoundingly with oral antiviral therapy, is that fibrosis and even cirrhosis can regress—a concept that seemed revolutionary when I was a medical student—not only with HCV infection but with other liver diseases as well. This has raised the intriguing question of whether patients with cirrhosis regression documented with, for example, transient elastography, might have a sufficient decline in risk of HCC to obviate the need for ongoing surveillance. There is an impression that the risk does decline, but in my opinion not sufficiently to terminate surveillance at any finite time point. I recently had a patient with pretreatment F3 to F4 fibrosis whose transient elastography score fell to 5.0 kPa (F0-F1), yet still developed an HCC 6 years after achieving SVR in the absence of any other identifiable liver disease. Fortunately, the lesion was detected during ongoing surveillance, at a hopefully curable stage, with imaging at the usually recommended interval for HCC surveillance of every 6 months.

**G&H** What do you see looking forward for HCV treatment? What are the remaining unmet needs?

**IJ** Remarkably high rates of curability of HCV can be achieved with the present regimens, including one that has not been mentioned yet, the combination of sofosbuvir, velpatasvir, and the pangenotypic protease inhibitor voxilaprevir (Vosevi, Gilead). Given this, I do not readily foresee a drug developer investing what it takes to get a new regimen approved, but I cannot say it is impossible either. The unmet needs right now center on public health approaches to reducing the risks of transmission, identifying the still large number of people with HCV infection in the general population with effective screening approaches starting with both public and provider awareness of the need to screen, implementing recommendations for at least onetime screening for HCV in the general population, optimizing linkage-to-care strategies for diagnosed patients, and improving global access to care. In 2020, the Centers for Disease Control and Prevention recommended prenatal screening of all pregnant women for HCV, just as we have long done for hepatitis B virus.

**G&H** Are there any misconceptions about sofosbuvir or HCV treatment in general that you would like to clear up?

**IJ** There are none that I can readily think of because of the durability of the drug in clinical practice and its continued track record of efficacy and safety. Old ideas that patients with mild disease or normal alanine aminotransferase levels do not need treatment have long been relegated to obscurity. Every viremic patient should be treated. The idea that patients with acute HCV infection should be observed to see if they clear the virus spontaneously has been replaced by a general agreement that treatment should be started immediately. Another misconception, which I already discussed, is that virologic cure eliminates the future risk of HCC or the need for surveillance in patients with antecedent cirrhosis.

***Disclosures***

*Dr Jacobson has been a consultant and investigator with Gilead Sciences and a consultant with AbbVie.*

## Suggested Reading


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