The Ineffective Cure

Hepatitis C and the Drug That Never Got Its Chance

by

Theora Isobelle Wen Tiffney

A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Approved September 2020 by the
Graduate Supervisory Committee:

Robert Cook-Deegan, Co-Chair
James Collins, Co-Chair
Heather Ross
Matthew Chew

ARIZONA STATE UNIVERSITY

December 2020

ABSTRACT

Hepatitis C is an infectious disease that affects 71 million people worldwide and causes liver failure and death if untreated. In 2013, a direct acting antiviral drug, sofosbuvir, revolutionized treatment of the disease. Sofosbuvir showed immense promise, but the high price point at which it was launched created access barriers that prevented it from reaching its full public health potential. By 2016, fewer than 1% of Hepatitis C patients worldwide had received treatment. In the United States (US), concerns about the cost of the drug led public and private payers to implement rationing and treatment restrictions that prevented some of the most vulnerable populations from accessing Hepatitis C treatment at all. Through interviews with researchers, patients and providers, and a literature review of grants, patents, papers, court documents, and news articles, I examine the history of sofosbuvir with attention to the ways in which federal funding practices and intellectual property law encouraged the high initial pricing of the drug. I then examine the impact of this drug on healthcare systems in the United States and abroad, and discuss how the fragmented nature of the United States healthcare system has exacerbated price-based barriers to access. Finally, I discuss intellectual property laws as potential mechanisms to increase access. My study underscores how the political reluctance to use well-established federal funding and intellectual property laws has resulted in a drug development system that delivers medications that are so highly priced that the fragmented US healthcare system cannot compensate for the expense. This leads to low access and poor public health outcomes, and a continued failure to contain or control diseases for which effective therapies exist.

DEDICATION

To my committee, friends, and family, who supported me through this process with kindness and humor.

ACKNOWLEDGMENTS

Many thanks to my committee for support both academic and financial: my co-chairs Dr. Robert Cook-Deegan, and Dr. James Collins, and Dr. Heather Ross and Dr. Matthew Chew. Thank you also to Sam Levinson for assistance in translating molecular biology and biochemical terms and procedures, to the staff of HepDart for making my attendance possible, and the people who kindly agreed to be consulted or interviewed.

Thank you, as well to my readers: Bruce and Robin Tiffney and E. K. Green, without whom this document would be significantly less coherent.

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER 1

THE INEFFECTIVE CURE

"What is there left to study about Hepatitis C?" asked the speaker. The audience responded with scattered, polite laughter.

It wasn't the first time I had heard that question that week. Many of the researchers at this conference had asked me some variation on it when I'd introduced myself. I was a graduate student studying the history of Hepatitis C Direct Acting Antivirals, a highly effective class of drug that made curing—and maybe even eliminating—a deadly liver disease within reach. This was a clinical research conference, and sitting in this room with me were many of the people integral to the development of one, or several, of these direct acting antivirals.

The date was December 9, 2019. The conference location: the Grand Hyatt Resort on Kauai, the "best hotel on the island", according to a local friend. Even in December, the air conditioning was set to stun. As soon as I walked out of the room onto the broad veranda where meals and the registration table opened onto a beautifully maintained garden, I ran into Hawaii's 'winter weather'—80 degrees, 80% humidity. Wild ginger and coconut palms waved in an ocean breeze, birds I was totally unfamiliar with sang high above, and slugs the size of my palm eased their way along walkways and walls. The sole concessions to the season were a series of large, artfully decorated Christmas trees, and a soundtrack of carols rendered on ukuleles. Within the Grand Ballroom, some of the most prestigious liver experts in the world talked about the greatest challenges in their fields. The focus, this year, was on Hepatitis B (an infectious disease, but one unrelated to Hepatitis C) and NAFLD/NASH—Non-Alcoholic Fatty Liver Disease and Non-

Alcoholic Steatohepatitis, which are noninfectious liver diseases that affect millions of people around the world.

In an extremely expensive resort (non-conference room prices run well above $700 a night) filled with pharmacologists and biochemists, it did seem there wasn't a lot left to study. The direct acting antivirals some of the conference attendees invented have incredible cure rates, with more than 90% of patients treated with them recovering completely. The biochemists' jobs were done. The victory lap was over. This conference was focused on the next big challenge. Or challenges.

And what a victory! Up until 2013, if you were diagnosed with Hepatitis C, you could look forward to liver failure or cancer—and eventually death, if you were not among the lucky few to spontaneously clear the disease, or to respond to the long-term, hugely uncomfortable interferon-based treatments that only cured about 60% of patients in the most responsive groups (that is, patients who had the right strain of the disease, and didn't have any other conditions like HIV—the chances of being cured dropped as low as 30% in other cases).

Death from Hepatitis C is horrific. As the liver fails, so does everything else. Nausea, diarrhea, inability to control the bowels, mental confusion, swelling of the body (called ascites), yellowing of the eyes and skin, lung and heart failure—before direct acting antivirals, this was the future that Hepatitis C patients could anticipate.

Many of the people in the ballroom with me helped to change that. Direct acting antivirals, or DAAs, were a game changer. The first few were toxic—but in 2013, a new DAA emerged on the market. It was called sofosbuvir, and if you combined it with the

old treatments, you saw 90+% of your patients recover. Treatment was still horrifically uncomfortable, but at least patients had a good chance of getting something from it.

In 2014, sofosbuvir was combined with another DAA, ledipasvir, which achieved 94% cure rates without any need for the old, uncomfortable treatments. A whole slew of other DAAs followed it, but sofosbuvir is still a vital part of many treatment regimens, or combinations of medications. Sofosbuvir and other DAAs can truly be said to have *cured* Hepatitis C.

So, by 2019, most of the researchers had moved on. As we attendees snacked on the excellent food provided by the conference—local pastries and coffee, guava and pineapple juice, local cheeses—they argued about new treatments and cell cultures for Hepatitis B (still uncured), and the non-infectious liver disease experts debated whether a clinical treatment is even appropriate for fatty liver disease, given that the greatest risk factor is obesity. On the last night of the conference, we all shuttled to the adjacent hotel to attend a luau, which was included in the conference ticket. We stared in rapt attention at the performers, got in each other's ways at the buffet tables and open bars, the sound of the ocean a constant background to the talk, laughter, and music.

The next evening, I boarded a red-eye back to Phoenix, where I was greeted by a cold desert, bad traffic, a leaking roof, and the reality of Hepatitis C in most of the United States. At an interview after my return with a senior member of a harm reduction group for injection drug users in the Phoenix area, I mentioned the pervasive attitude at the conference, that Hepatitis C was a solved problem.

He laughed, bitterly. "No," he said, after a moment. "I mean, who are they talking about?"

For many people in the United States, sofosbuvir and its relatives may as well not exist. Before COVID-19, Americans were still dying of Hepatitis C in greater numbers than any other infectious disease, more so than the next sixty-odd most common deadly infectious diseases. They're swelling up and vomiting and soiling themselves, they're moving through their lives in a haze of confusion and anxiety as the toxins that their livers can't filter out destroy their brains. From a public health perspective, sofosbuvir was an immensely promising drug that has not reached the majority of people it was intended to cure. The World Health Organization set viral hepatitis elimination goals earlier in the decade, and despite the existence of really effective drugs, few countries are on target. Few countries will hit the goal of elimination (90% diagnosis, 80% treatment) by 2030. The United States lags further behind than most.

The problem with Hepatitis C is that it affects some of the poorest, most disenfranchised people in the country—and in the world. Hepatitis C is primarily transmitted through infected blood. It can be transmitted through a needlestick injury. It can be transmitted through a contaminated blood transfusion or organ donation, or the reuse of a needle during a vaccination campaign. It can be transmitted by a tattoo needle, by sharing needles or other equipment used in injecting drugs, and it can be transmitted from mother to child during birth. It can also, far less commonly, be transmitted through sexual intercourse. Because of the ways it’s transmitted, the people most at risk for it are people who are already stigmatized.

The burgeoning Hepatitis C epidemic rides the coattails of the opioid crisis. Attempts to curtail prescription drug misuse drive patients to injectable drugs, and lack of

access to clean needles leads to needle reuse and transmission of Hepatitis C, HIV, and a host of other pathogens. The patients of the opioid epidemic are triply assailed—not just by chemical dependency, but by Hepatitis C and HIV, and by unsympathetic health and criminal justice systems that in many cases actively exclude them. Substance abuse disorder can exclude patients from treatment for Hepatitis C, and treatment for addiction does not yet meet the demand caused by the opioid epidemic.[1]

A few weeks before my departure for Kauai, I visited the offices of one harm reduction organization in the Phoenix area in company with one of my colleagues, who specialized in treatment access for people the organization served. A vicious hailstorm had rolled in, and getting indoors, and out of the stinging cold, was an instant relief. The room smelled faintly antiseptic. Blocking the entry was a picnic table with a disposable seafoam green tablecloth and an array of medical supplies. Two women stood around it, chatting as they prepared for a medical procedure. Both greeted my colleague with small smiles and nods, before returning to their work.

We squeezed around their table to greet a large, bearded man with a firm handshake. I introduced myself and my research—the study of the history of Hepatitis C drugs and the current access situation. His mouth twisted wryly.

"Hepatitis C?" he said. "Everyone here has it." Then, as if he were correcting himself, "Well, about 95% of injecting drug users in Phoenix."

Stopping Hepatitis C is not so simple as stopping opioid use. Our health systems are, if anything, designed to maximally exclude anyone with substance use disorder; few

[1] Beth Macy, *Dopesick: Dealers, Doctors, and the Drug Company That Addicted America* (Little, Brown, 2018).

even seek treatment, because they assume they won't get it. In my current home of Arizona, while the state has managed to get direct acting antivirals at a lower than average price for its Medicaid patients, sobriety requirements remain. These restrictions require individuals to demonstrate a certain amount of time abstinent from highly addictive substances. But since people who inject drugs are the people both at highest risk of catching and spreading the disease, it's not just their lives and wellbeing at stake. It's the lives and wellbeing of everyone in their social groups. They're possibly the most vital people to treat to stop spread, and one of the most undertreated populations. And yet, they're the ones facing the highest barriers to treatment.

The programs that assist people who inject drugs, such as the harm reduction program I visited, recognize that these people are the ones most in need of care. Nationwide, these programs have been coming up with strategies to get around onerous requirements and get these individuals the treatments they need however they can, sometimes in open defiance of treatment requirements. These requirements are actually illegal under the federal laws that govern Medicaid—if a state Medicaid program provides prescription drug coverage, it cannot erect barriers to patients who need those drugs—but many states, including Arizona, have them anyway. After talking to people at the harm reduction program, I called Arizona's state Medicaid, the Arizona Health Care Cost Containment System, to ask about the reasons for these barriers. Though I contacted with a specialist there, my questions were never answered.

One practitioner told me about "pee parties" where their colleagues would gather to substitute their own urine for those of their patients. Their clean urine allows their neediest patients to pass the drug tests required by law to access treatment. Another spoke

of going abroad to buy Hepatitis C medications in bulk so that, even after patients were told by their insurance providers they absolutely would not be treated, they could get the medical care they needed.

But in Hawaii, sofosbuvir's creators protested that this wasn't their problem. "We're at a conference of chemists and clinicians," another graduate student told me. "This is a public health problem." The implication was, *this isn't the right place to discuss the people dying of Hepatitis C. This isn't our fault.* Blame seemed to have a way of falling elsewhere. It was health insurance companies, state bureaucracies, the United States health system. The researchers and clinicians had done their jobs. They wanted to be recognized for it. They saw the backlash as intensely unfair. And those insurance companies, states, and practitioners pointed the finger right back at the companies creating and selling direct acting antivirals. They'd priced it too high.

And whoever's fault it was, people were dying.

When that first extremely effective direct acting antiviral, sofosbuvir, was released in 2013, the list price was $84,000 per course of treatment. Around the US, payers panicked, and states struggled to make the drug available to their beneficiaries with Hepatitis C. Sometimes, their efforts were unsuccessful. The price of treating every prisoner in Missouri with Hepatitis C far outstrips the entire healthcare budget for the state's prison system.[2] In Louisiana, treating just the Hepatitis C patients would have consumed the state's entire Medicaid budget.[3] Around the US, and around the world,

[2] Alex Smith, "Missouri Faces Costly Dilemma: How To Treat Inmates With Hepatitis C?," *NPR.Org*, January 19, 2018, https://www.npr.org/sections/health-shots/2018/01/19/578425032/missouri-faces-costly-dilemma-how-to-treat-inmates-with-hepatitis-c.
[3] Carolyn Y. Johnson, "Louisiana Considers Radical Step to Counter High Drug Prices: Federal Intervention," *Washington Post*, July 3, 2017,

communities are still faced with a conundrum: the cure for the disease exists, but the money to access it does not.

17,253 people died of Hepatitis C in 2017 in the United States.[4] Experts say this is likely a low estimate, because a person who dies from Hepatitis C may have their death attributed to liver failure instead.[5] Viral Hepatitis kills more people worldwide than even HIV. Hepatitis B's numbers can be reduced through vaccination; no vaccine exists for Hepatitis C. [6]

If the buck doesn't stop with the people who made the pricing decision for this drug, where does it stop? With state Medicaid programs that don't have enough money in their entire budgets to treat the Hepatitis C patients for whom they are responsible? With pharmacy benefits managers? With the whole American healthcare system which isn't a unified system? What about the ways we fund research, which leave so many open doors for the taxpayer to pay for a drug twice (once via federal grants, again when getting treated)? And then there is the objection that, even if the drug costs too much for many programs to support, isn't that just the price we pay for good innovation?

The answers to these questions are the central story of sofosbuvir, the miracle drug that never got a chance. A taxpayer-funded clinical marvel, sofosbuvir's public health potential has been stifled by the ambitions of its creators, the American health

---

https://www.washingtonpost.com/business/economy/louisiana-considers-radical-step-to-counter-high-drug-prices-federal-intervention/2017/07/03/456b99f6-4a59-11e7-a186-60c031eab644_story.html.

[4] Centers for Disease Control and Prevention, "Hepatitis C Questions and Answers for Health Professionals | CDC," September 10, 2019, https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm.

[5] Centers for Disease Control and Prevention, "Viral Hepatitis Surveillance - United States, 2016" (Centers for Disease Control and Prevention, 2016); Centers for Disease Control and Prevention, "Hepatitis C Questions and Answers for Health Professionals | CDC," accessed December 31, 2019, https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1.

[6] World Health Organization, "Progress Report on Access to Hepatitis C Treatment: Focus on Overcoming Barriers in Low- and Middle-Income Countries" (World Health Organization, 2018).

system, and our persistent willingness to allow entire social classes to become disposable. It's a poignant demonstration that we have let the lessons of HIV/AIDS go unlearned.

"What is there left to research about Hepatitis C?"

Why is a disease with a cure a leading killer in the United States?

Why does the American pharmaceutical industry keep giving us powerful medications that are effectively nonexistent for many people because they aren't affordable?

And most importantly, not only for Hepatitis C patients, but for any patient who can't afford medications—*how do we stop this?*

The good news: we have powerful policy tools already at our disposal, even if they have not been used in the pharmaceutical industry for decades—or at all. The even better news is that we can likely use these policy tools without cutting into the profit margins so essential for innovation in the pharmaceutical realm.

The bad news is that the systems that encourage high drug pricing, and the problems that this pricing causes, have the force of inertia behind them. They work just well enough (for example, competition in the market has driven sofosbuvir's price down to about $24,000 per course of treatment, though access barriers remain significant) to decrease the urgency of their resolution. And there is a great deal of money to be made in them continuing as they are.

This work follows the history of sofosbuvir, that first effective, safe, direct acting antiviral. I chose sofosbuvir because of its integral role in treatment regimens, because of its high initial price point, and because, of all the Hepatitis C drugs on the market, it has one of the clearest histories of publication. It has also attracted the most attention,

becoming a poster child for apparent corporate greed alongside the Epi-Pen and Martin Shkreli (the CEO who hiked the price of an existing HIV drug, Daraprim, by about 5,000%)[7], a demonstration of all that is wrong with the pharmaceutical industry today.

While researching the history of this drug, I conducted a comprehensive literature review of the basic academic research and clinical literature related to sofosbuvir, the patent literature, National Institutes of Health funding records, Congressional records, and news articles. I also contacted the researchers listed as authors on publications and patents and interviewed them. To demonstrate the impacts of the drug on patients, providers, and health systems, I interviewed patients, providers, and health-related organizations, and integrated my findings with news stories and reports from health organizations, such as the World Health Organization.

Many Americans feel prescription drug prices are too high, and indicate they do not trust pharmaceutical companies to price their products fairly. A quarter of Americans find it difficult to afford their prescription drugs. About a third don't follow their doctor's directions on how to take their medicine, or don't take it at all, due to how much it costs.[8] NPR called the 2010s "A Decade Marked By Outrage Over Drug Prices".[9] The story of sofosbuvir shows, from start to finish, how drugs get priced so highly that the diseases they cure continue to rage, unabated.

---

[7] Andrew Pollack, "Drug Goes From $13.50 a Tablet to $750, Overnight," *The New York Times*, September 20, 2015, sec. Business, https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html.

[8] Lunna Lopes, Bryan Wu, and 2019, "KFF Health Tracking Poll – February 2019: Prescription Drugs," *The Henry J. Kaiser Family Foundation* (blog), March 1, 2019, https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-february-2019-prescription-drugs/.

[9] Sydney Lupkin, "A Decade Marked By Outrage Over Drug Prices," *NPR.Org*, December 31, 2019, https://www.npr.org/sections/health-shots/2019/12/31/792617538/a-decade-marked-by-outrage-over-drug-prices.

Drug pricing is still a crisis even during health emergencies. At the time of this writing (August 2020) the pandemic caused by the novel coronavirus, SARS-2, is spiking once again in some areas following hasty, economically-driven reopenings across the United States. President Trump's refrain, "We can't let the cure be worse than the disease" has been proven utterly false. The struggling economy is reacting to rising COVID-19 cases more than the restrictions implemented to contain them.[10] The initial understanding that the virus primarily affected people who were elderly or had existing medical conditions has likewise been demonstrated false, as young people can both spread and succumb to the disease.[11] Yet, the assumption that only the people we could afford to lose would die of COVID-19 has been implicit throughout political attempts to handwave the pandemic's impact. It is much the same as we saw with HIV/AIDS. It is much the same attitude that has allowed Hepatitis C to rage quietly, uncontrolled, across this country.

COVID-19 has yet another similarity to Hepatitis C. Gilead Sciences, the producer of Solvaldi, manufactures another drug, remdesivir, that shows moderate promise for treating moderate cases of COVID-19, for which they are charging a high price ($3,120 on private insurance).[12] Anxiety is growing about the potential price of a vaccine. The resultant outrage during a national emergency may in fact encourage

[10] Ann Saphir and Howard Schneider, "Fed Chief Says Coronavirus Surge Slowing U.S. Economic Recovery," *Reuters*, July 29, 2020, https://www.reuters.com/article/us-usa-fed-idUSKCN24U2VB.
[11] Alistair Gee, "Lives Cut Short: Remembering Health Care Workers In Their 20s Killed By COVID-19," *NPR.Org*, August 13, 2018, https://www.npr.org/sections/health-shots/2020/08/13/901720066/lives-cut-short-remembering-health-care-workers-in-their-20s-killed-by-covid-19; William Wan and Moriah Balingit, "WHO Warns Young People Are Emerging as Main Spreaders of the Coronavirus," *Washington Post*, accessed August 28, 2020, https://www.washingtonpost.com/health/who-warns-young-people-are-emerging-as-main-spreaders-of-the-coronavirus/2020/08/18/1822ee92-e18f-11ea-b69b-64f7b0477ed4_story.html.
[12] Sydney Lupkin, "Remdesivir Priced At More Than $3,100 For A Course Of Treatment," *NPR.Org*, June 29, 2020, https://www.npr.org/sections/health-shots/2020/06/29/884648842/remdesivir-priced-at-more-than-3-100-for-a-course-of-treatment.

significant reform. But that reform cannot be specific to COVID-19. Hepatitis C will still be here when COVID-19 is tamed.

The thesis of this dissertation is this: The current systems by which we fund, develop and sell medications all encourage pricing that makes those drugs unavailable to the patients who need them. Even if the prices of these medications decline with time (due to competition, the release of generics by the patentholder, or, more rarely, public pressure), the structures that exclude patients from access remain, continuing the access crisis long after the original problem (drug price) is remedied.

Paul Farmer, a medical anthropologist, physician, prominent global health equity activist, and one of the founders of the healthcare delivery nonprofit Partners in Health, wrote of similar circumstances that HIV patients face:

> *"Their sickness is a result of structural violence: neither culture nor pure individual will is at fault; rather, historically given (and often economically driven) processes and forces conspire to constrain individual agency. Structural violence is visited upon all those whose social status denies them access to the fruits of scientific and social progress."*[13]

This is true of Hepatitis C patients, as Farmer observed in an editorial in the Washington Post shortly after the release of sofosbuvir.[14] Hepatitis C spreads in the same ways as HIV does. It affects the same people, people who are vulnerable to the disease because of their socioeconomic status. Once they become ill, they remain ill because of social and economic barriers to treatment, such as sobriety requirements and stigma, or the lack of funding for the health programs that should serve them. This is structural

[13] Paul Farmer, *Infections and Inequalities: The Modern Plagues* (University of California Press, 2001), 79.
[14] Paul Farmer, "The Global AIDS Response Can Help in Fighting Hepatitis C," *Washington Post*, February 12, 2014, sec. Opinions, https://www.washingtonpost.com/opinions/the-global-aids-response-can-help-in-fighting-hepatitis-c/2014/02/12/aa76ecc2-89e3-11e3-833c-33098f9e5267_story.html.

violence, violence that is perpetrated not by an individual or individuals, but the by the very structure of the societies in which we exist. It's the product of government policy, and of historical disenfranchisement, and of economic pressures, but the injury and death it inflicts are just as tangible as the results of a physical attack.

In the case of Hepatitis C, dismantling the system that creates low-access situations requires change in how we distribute federal funding, in how we enforce the existing laws governing federal funding, and in whether we choose to enforce existing laws intended to provide fair access to innovation to the American people.

Sofosbuvir is a lesson in the ways in which this cycle plays out. It exemplifies a perfect storm of a high-priced drug colliding with strained healthcare systems and a federal government unwilling to invoke the laws intended to ameliorate barriers to medication access. The history of sofosbuvir reveals the ways in which we can intervene, and what happens when we do nothing.

CHAPTER 2

THE CRYPTIC VIRUS

In the summer of 1793, fever gripped Philadelphia.

The United States was an infant nation, Philadelphia its capital—Congress wouldn't move to Washington DC until 1800. Congress was already adjourned for the summer, but most of members still in town left quickly as the fever spread. Initially, residents blamed spoiled coffee rotting on the docks for the illness. Then, fingers were pointed at the sources of other foul odors—miasmas. But the real culprit lived in stagnant water—barrels, pots—anywhere a little pool might collect and sit undisturbed. The summer went on. Philadelphians died, their skin yellow, their vomit black and grainy, and all the while, in those pools, mosquito eggs matured into larvae, and then into biting, disease-spreading adults.[15]

These mosquitos were probably *Aedes agypti. Aedes agypti* are large, with hindlegs banded in handsome black and white. They can breed in a seemingly endless number of places. Modern public health agencies warn the public to empty water even from old tires—those pools are all that *Aedes agypti* larvae need to complete their weeks of development.[16] And public health agencies have good reason to warn about *Aedes agypti. Aedes agypti* transmit Zika. They transmit Dengue. And in that sweltering, humid summer of 1793, they transmitted yellow fever throughout Philadelphia.

[15] J.M. POWELL et al., *Bring Out Your Dead: The Great Plague of Yellow Fever in Philadelphia in 1793* (University of Pennsylvania Press, 1993), https://www.jstor.org/stable/j.ctt6wr9c9.
[16] Arizona Department of Health Services, "AZDHS | Protection from Mosquitoes," Arizona Department of Health Services, accessed June 8, 2019, http://www.azdhs.gov/preparedness/epidemiology-disease-control/mosquito-borne/protection-from-mosquitoes/index.php.

Yellow fever causes fevers, headache, vomiting, and exhaustion. For people who have the mild version of the disease, these symptoms go away after a week or so. For the unlucky 14% of people who develop a severe case of the disease, they may feel better for a few hours, maybe even a day. Then, they get even sicker—horribly, even fatally so. They develop a punishing high fever, the yellow skin for which the disease is named, and internal bleeding. This bleeding causes black, grainy vomit—a result of bleeding in the stomach. The mortality rate for this severe form is 30 – 60%.[17]

Doctors in 1793 didn't know what to do with the illness. The standard remedies of purging and bleeding, of feeding patients a wide variety of concoctions in the desperate hope that one might cure the stricken, worked unpredictably. Sometimes (and to our modern understanding of medicine, unremarkably) they made the patients worse or killed them. Sometimes, they seemed to save the patients. Sometimes, the patients responded, then became even sicker. In the end, the city simply had to wait it out. At the end of that summer, at least 5,000 Philadelphians were dead.

Yellow fever is still with us. In 2016, it caused an outbreak in Angola, the Democratic Republic of the Congo, and Uganda. It was a remarkably large outbreak, stanched by a massive vaccination campaign.[18] The ability to vaccinate, coupled with improved supportive care, are the reasons that Yellow Fever no longer elicits the dread

[17] Centers for Disease Control and Prevention, "Yellow Fever: Symptoms, Diagnosis, & Treatment," Centers for Disease Control and Prevention, January 16, 2019, https://www.cdc.gov/yellowfever/symptoms/index.html.
[18] World Health Organization, "WHO | Yellow Fever Outbreak Angola, Democratic Republic of the Congo and Uganda 2016-2017," WHO, February 14, 2017, http://www.who.int/emergencies/yellow-fever/en/.

for us as it did the denizens of Philadelphia in 1793. But even now, there is no cure. Prevention and vaccination are the only weapons we have.[19]

Yellow Fever isn't the only big name in the family of viruses known as the *flavaviridae*. Remember the panic about Zika at the 2016 Olympics in Rio, and the pictures of infants with microcephaly caused by the virus? Zika is a flavivirus. How about West Nile Virus in the early 2000s? West Nile is also a flavivirus.

Hepatitis C, too, is a flavivirus, though in a different genus from those headliners. Yellow Fever, Zika, and West Nile are in the genus *Flavivirus.* To get them, you have to be bitten by a mosquito that bit a patient with the disease. But Hepatitis C is in the genus *Hepacivirus*, which can be passed between hosts directly and attacks the liver. They don't need an insect to travel between humans (or other mammals).[20]

But the two groups of viruses do share similar genetic material, organized in pretty much the same way. These parallels in organization allowed researchers to identify regions to target with drugs in Hepatitis C. Early papers after the virus's discovery compared its genome to that of yellow fever, comparing locations of nonstructural proteins (the regions where information about replication is encoded) between the two viruses.

Not all hepatitis viruses are Flaviviridae, and they're not related. Hepatitis B and Hepatitis A are caused by different viruses that are not related to Hepatitis C. They're all called "hepatitis" because of the damage they do to the liver, which causes patients to

[19] World Health Organization; Centers for Disease Control and Prevention, "Yellow Fever: Symptoms, Diagnosis, & Treatment."
[20] Peter Simmonds et al., "ICTV Virus Taxonomy Profile: Flaviviridae," *The Journal of General Virology* 98, no. 1 (January 2017): 2–3, https://doi.org/10.1099/jgv.0.000672.

display the symptoms. This is because before they could be identified as different viruses, it wasn't clear whether they were so similar because of what organ they affected (which was the correct answer) or because they were related. Hepatitis A was easiest to distinguish, because it causes a short course of illness and is transmitted by what the medical field charmingly calls the "fecal-oral route", through the ingestion of food that has been contaminated with the feces of someone infected with the disease. But early studies lumped Hepatitis B and C together as "transmissible hepatitis". Earlier still, because a failing liver causes the skin and eyes to turn yellow (a symptom known in medical circles as jaundice), they were known as homologous serum jaundice.[21] This referred to a jaundice that happened after a patient had received a blood transfusion.

Hepatitis C remained lumped in with the other forms of hepatitis for so long because it was a difficult virus to identify. All of *Flaviviridae* are small. The Hepatitis C virus is no exception. When it became clear that it wasn't Hepatitis A or Hepatitis B (because patients with it tested negative for both other viruses), it was called Non-A Non-B Hepatitis—a liver condition that could be transmitted from person to person, not caused by any known virus.

Hepatitis A and B were the only known types of transmissible hepatitis until the 1970s. There weren't any laboratory tests for them at first, so whether someone had hepatitis, and whether it was Hepatitis A or Hepatitis B, was diagnosed purely by symptoms, and the patient's history. If it were a short, sudden illness, and if the patient had probably eaten something recently contaminated with the virus, it was Hepatitis A. If

[21] Robbins, Stanley L., *Textbook of Pathology With Clinical Application*, Second Edition (Philadelphia: W. B. Saunders Company, 1962).

the patient had had a blood transfusion, it was probably Hepatitis B, which had a longer incubation period. The fact Hepatitis B was transmitted by infected blood gave it the alternate name of "serum hepatitis," serum being the part of the blood left behind after clots form.[2223]

Hepatitis B was the key to the discovery of Hepatitis C. Both infectious diseases are transmitted through exposure to contaminated blood, and both can take a while to manifest after infection. Serum hepatitis was a scary prospect in the 1960s. There wasn't a way to screen for it in the blood supply; tests for Hepatitis B would only become available much later in the decade. Tests for Hepatitis C wouldn't be available until the early 1990s.

In 1966, an article titled *Post-Transfusion Hepatitis: A Serious Clinical Problem* appeared in the journal *California Medicine*, sounding the alarm about serum hepatitis and urging greater caution in blood transfusions. It encouraged surgeons to limit the number of transfusions to lower the risk of transmission of hepatitis during surgeries. It also pointed an accusing finger at blood from prisoners or from Skid Row in Los Angeles—disenfranchised groups of people we now know to be at high risk for the illness.[24]

What the author described in the 1966 paper certainly sounds a lot like Hepatitis C. The hepatitis was definitely not Hepatitis A. It wasn't transmitted through contact with

---

[22] Blake Flournoy, "What Is Serum?," Sciencing, July 20, 2018, https://sciencing.com/what-is-serum-4673561.html.
[23] Leonard B. Seeff, "The History of the 'Natural History' of Hepatitis C(1968–2009)," *Liver International : Official Journal of the International Association for the Study of the Liver* 29, no. 0 1 (January 2009): 89–99, https://doi.org/10.1111/j.1478-3231.2008.01927.x.
[24] J. Garrott Allen, "Post-Transfusion Hepatitis—A Serious Clinical Problem," *California Medicine* 104, no. 4 (April 1966): 293–99.

feces and urine, and didn't seem to be transmitted if potentially infectious material were administered orally. It was therefore iatrogenic, or transmitted in healthcare settings where patients received blood transfusions.[25] There's a long period between infection and symptoms. The author notes that many cases are probably undetected, a familiar problem to those studying Hepatitis C now. Many, many cases go unreported even with blood tests to diagnose it.

The identification of Hepatitis B, and the development of tests for it in 1974, made it possible to demonstrate that all of these cases of bloodborne hepatitis weren't caused by the same virus. Eager to screen for and study this new condition, researchers began testing patients for indications that their livers were compromised years after surgeries that had involved blood transfusions. They then tested those patients to see if they reacted to a compound specific to the surface of Hepatitis B, called Hepatitis B antigen, to demonstrate that this new virus was causing a transmissible hepatitis.

In August of 1974, a group of hepatologists and pathologists published a letter in the prestigious journal *Lancet.* They had a number of serum hepatitis patients—36 from their test group of 204, none of whom was reacting to Hepatitis B antigen. They didn't have Hepatitis A—the histories of their illness didn't match the way that Hepatitis A worked. They didn't have the right risk factors. Onset seemed to be late. But they definitely had hepatitis, and their liver functions were compromised. More provocatively, they had all received transfusions while undergoing various heart surgeries at New York University Hospital. [26]

---

[25] Allen.

[26] AlfredM Prince et al., "LONG-INCUBATION POST-TRANSFUSION HEPATITIS WITHOUT SEROLOGICAL EVIDENCE OF EXPOSURE TO HEPATITIS-B VIRUS," *The Lancet*, Originally

Those surgeries were between 2 and 5 years in the patients' past. It's possible that not all the Hepatitis C cases were detected, since Hepatitis C virus can lie dormant in the body for decades. But since Hepatitis A and B could be ruled out, the researchers suspected that this was evidence of the existence of a Hepatitis C virus. [27]

It took a while before the rest of the field accepted their name for the virus. Non-A, Non-B Post-Transfusion Hepatitis (NANBH) was the term of choice well into the 80s. It was out there. It existed. And it was very difficult to pin down what was causing it. At least the method of transmission seemed fairly clear. People who developed NANBH had often received blood transfusions. So the people studying it suspected that the condition was transmitted through direct blood-to-blood contact.

But whatever it was, it was a difficult virus to study. Not only was it very small, but the quantity of virus present in infectious bodily fluids was extremely low. To make it worse, whatever the virus was, it was diverse. Different laboratories reported different antigen-antibody interactions associated with the illness, which made detecting a single culprit difficult. Antigens are molecules on the surface of a virus that antibodies, parts of the human immune system, can recognize and attack.[28] Different antigens made people wonder if they were really looking at a single, genetically distinct, species of virus.[29] Today, we recognize taxonomic differences—different subspecies of Hepatitis C—in this

published as Volume 2, Issue 7875, 304, no. 7875 (August 3, 1974): 241–46, https://doi.org/10.1016/S0140-6736(74)91412-3.

[27] Prince et al.

[28] Mark A. Feitelson, *Hepatitis C Virus: From Laboratory to Clinic* (Cambridge, UNITED KINGDOM: Cambridge University Press, 2002), http://ebookcentral.proquest.com/lib/asulib-ebooks/detail.action?docID=201762; The Editors of Encyclopaedia Britannica, "Antibody | Definition, Structure, Function, & Types," in *Encyclopedia Britannica*, accessed August 28, 2020, https://www.britannica.com/science/antibody.

[29] Feitelson, *Hepatitis C Virus*.

genetic diversity. In the 1970s and 1980s, it was simply another confusing aspect of the disease.

The next step in figuring out what the virus was and how it could be treated was to study it in animals, outside human patients. Animal models, often known as *model systems*, allow scientists to do studies that would be too risky or uncomfortable to do with humans.

In 1978, a series of studies was conducted to test if Non-A, Non-B Hepatitis could be transmitted to chimpanzees, a common experimental animal. The studies followed a similar pattern; administer infectious material to a small number of chimpanzees, then rule out other potential causes for a reaction, if disease symptoms appeared.[30]

In one study, chimpanzees were injected with blood plasma or serum from human patients with NANB hepatitis—ones who had acute illness, or chronic cases who had been ill with it for some time. While the animals appeared to recover, they did all develop high levels of a liver enzyme called alanine aminotransferase that appears in the blood when the liver is damaged.[31] These levels were consistent with a hepatitis infection. The chimpanzees also developed a range of the symptoms of hepatitis. None of them reacted to Hepatitis A or Hepatitis B antigens, showing that their hepatitis was due to a different virus.[32]

---

[30] Blaine Hollinger et al., "Non-A, Non-B Hepatitis Transmission in Chimpanzees: A Project of the Transfusion-Transmitted Viruses Study Group," *Intervirology* 10, no. 1 (1978): 60–68, https://doi.org/10.1159/000148969.
[31] Marc S Orlewicz, "Alanine Aminotransferase: Reference Range, Interpretations, Collection and Panels," December 13, 2018, https://emedicine.medscape.com/article/2087247-overview.
[32] HarveyJ. Alter et al., "TRANSMISSIBLE AGENT IN NON-A, NON-B HEPATITIS," *The Lancet*, Originally published as Volume 1, Issue 8062, 311, no. 8062 (March 4, 1978): 459–63, https://doi.org/10.1016/S0140-6736(78)90131-9.

Knowing the disease could infect chimpanzees was an advantage, but not a solution. While research can be done with animals that can't be done with humans, there are serious drawbacks. When choosing an animal to use as a model system, researchers have to walk a narrow line between complexity of the animal (and similarity to humans, in medical research), the ease of keeping them, and the ethics of experimenting on that organism. When it comes to chimpanzees, the ethics are complex.

In one sense, chimpanzees are excellent model systems because they're closely related to humans. We share a recent common ancestor with the chimpanzee, and chimps and bonobos are the closest evolutionary relatives we have.[33] This means if you observe something happening in a chimp in response to, say, an infection, it's very likely that there will be the same, or a very similar, reaction from a human. Even in mice and rats, which are very popular model systems, treatments can fail when they come to clinical trials because rodent immune systems are just different enough from those of humans to throw a serious wrench into the works.

Chimpanzees are also a terrible animal model because they're closely related to humans. There are ethical considerations. Chimpanzees are intelligent, and the more intelligent an animal, the more difficult it is to justify using it for experimental purposes, because the potential for emotional suffering and physical damage becomes greater. Because of this, chimpanzees require a great deal of infrastructure to maintain. They need ways to entertain themselves. To socialize. They are also expensive and long lived. Most

[33] Ann Gibbons, "Bonobos Join Chimps as Closest Human Relatives," *Science | AAAS*, June 13, 2012, https://www.sciencemag.org/news/2012/06/bonobos-join-chimps-closest-human-relatives.

of the early research on Hepatitis C was done in chimpanzees, because they were the only animals that could support the virus outside of humans.

However, while having some model system was an immense advantage, researchers needed to be able to grow the virus in cell culture as well. Why use cell cultures? The central advantage is the control that cell cultures give a researcher. Animal bodies are constantly trying to regulate themselves to maintain a stable internal environment, a process called homeostasis. This means they're making lots of little adjustments all the time. In short, the conditions the cells exist under within an animal aren't constant, which can make it difficult to consistently reproduce the same results at different times or in different animals. That consistency is absolutely vital in testing medical treatments for a disease. Eventually, you do need to find out if a treatment works in a living animal. But when you're less focused on the interaction between animal and virus, and you're looking at the basic biology of the virus, it's much more helpful to have it in an environment where you can be sure things like the temperature are staying constant.[34]

As a result, Hepatitis C had to be identified and grown in a cell culture before scientists could start working on a cure. And identifying the actual virus was proving hard enough. Remember the genetic diversity of Hepatitis C? This diversity was one of the major stumbling blocks. If a chimpanzee that had recovered from one bout of NANB were reinfected using another sample that had been collected from a different source (such as a different human patient), it would become sick again. In effect, an animal

[34] María-Teresa Arango et al., *Cell Culture and Cell Analysis* (El Rosario University Press, 2013), https://www.ncbi.nlm.nih.gov/books/NBK459464/.

could get NANB more than once.[35] This was linked to the wide diversity of antigens observed in NANB's antigens. New antigens meant the body pretty much had to start from square one in recognizing and attacking the virus.

It wasn't until 1989 that the culprit behind NANB Hepatitis was finally unmasked. A group of researchers at the Chiron Corporation in California took a molecular approach, constructing a complementary DNA (cDNA) clone library from infectious material using a specific virus that eats bacteria (a bacteriophage—phage means 'to eat'). The bacteriophage used the DNA to express certain surface proteins that a potential virus might bind to, if they matched that virus's genetic sequence.

The researchers made a large number of these cDNA clones. They then combined them with concentrated infectious material and waited to see what, quite literally, stuck.

In the case of cDNA clone 5-1-1, something did.

The Chiron Corporation researchers had a lead. But the infectious material, in this case blood serum, also had lots of other DNA floating around in it. How could you tell for sure that clone 5-1-1 wasn't reacting to the host's DNA, rather than that of the infectious agent?

The researchers tested this by introducing 5-1-1 to human DNA and chimpanzee DNA that wasn't from infected hosts. The clone didn't try to attach to either, which meant whatever it was attaching to, it wasn't human or chimpanzee—and wasn't present in a body that wasn't infected with the disease.

They then tested clone 5-1-1 with RNA extracted from the infected liver of a chimpanzee. The clone attached to the RNA from the liver, as it had with the RNA

[35] Feitelson, *Hepatitis C Virus*.

floating around in the blood serum. It didn't react to RNA from uninfected livers. The evidence that this was a clone of the virus they were looking for began to seem solid.[36]

Examination of what clone 5-1-1 encoded seemed very similar to two families of viruses: the Flavaviridae, and the Togaviridae. Further refinement would come later, as NANBH (quickly dubbed Hepatitis C) was further studied and characterized. Regions of the virus's genome were compared to those of yellow fever. While the new virus was very different from existing Flaviviridae, there were some homologies—or similarities—between the two viral genomes. The Hepatitis C sequence was much closer to the sequences of Flaviviridae than any other family of viruses. This was enough to put Hepatitis C firmly in the family, a relative to the viruses that caused yellow fever and dengue.[37]

Sequencing and comparing the virus to other viruses allowed scientists to understand which regions of the virus's genome were responsible for which functions. They found structural and nonstructural coding regions.[38] Structural regions code for the basic shape of the virus; nonstructural proteins handle replication. Nonstructural proteins are important in creating drugs to treat viruses. Disrupt or stop the replication of a virus, and the infection can be stopped.

Another boon of identifying the virus was that tests could be designed to detect it in blood samples. Since so many Hepatitis C infections seemed to come from blood

---

[36] Q. L. Choo et al., "Isolation of a CDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome," *Science* 244, no. 4902 (April 21, 1989): 359–62, https://doi.org/10.1126/science.2523562.
[37] Q. L. Choo et al., "Genetic Organization and Diversity of the Hepatitis C Virus.," *Proceedings of the National Academy of Sciences* 88, no. 6 (March 15, 1991): 2451–55, https://doi.org/10.1073/pnas.88.6.2451.
[38] Michael Houghton et al., "Molecular Biology of the Hepatitis C Viruses: Implications for Diagnosis, Development and Control of Viral Disease," *Hepatology* 14, no. 2 (1991): 381–388.

transfusions or organ transplants, this was a major step in slowing its spread. It meant the blood supply could be screened, and donations that had the virus could be discarded. By 1992, it was common practice in the United States to screen donated blood for Hepatitis C. Thanks to this, if you received a blood transfusion after 1992 in the US, you are not at risk for Hepatitis C from that transfusion.

Being able to detect and remove contaminated blood products and organ donations cut off a major route of transmission for Hepatitis C, and decreased the number of people who were exposed. A cure was still needed, but Hepatitis C might have faded into obscurity within a few years. It might have become a disease that only affected older people who'd received risky blood donations or organ transplants, or gotten the disease from their mothers.

But that's not what happened. In the early 1990s, another health crisis began—and Hepatitis C found a new way to travel, hitching a ride on the needles of the victims of the opioid crisis.

CHAPTER 3

HEPATITIS C GETS ITS BIG BREAK

Even as Hepatitis C's spread in the blood supply came to an abrupt halt, its new route of transmission ramped up: opioid use.

When Hepatitis C was first identified, the virus primarily spread through healthcare settings, traveling in contaminated blood and organs that couldn't be tested. That's why a major risk factor for Hepatitis C was blood transfusions before it became possible to screen for the disease in the blood supply. Contaminated blood transfusions are why a large number of the people in the US who have Hepatitis C are 65 or older. It's also *part* of the reason that Hepatitis C is particularly prevalent among veterans. As a result, people over 65 are highly encouraged to seek testing for the disease.

The story of Hepatitis C in countries that could afford to test their blood supplies might have fizzled to a close, if it hadn't been for a new risk factor, the opioid epidemic, which is a common reason that younger people get Hepatitis C. Like HIV, Hepatitis C can be passed from person to person by contaminated needles. Rather than helping curb opioid abuse, measures such as making the pills themselves harder to use or less available drive people to riskier behaviors, such as injecting instead of swallowing or snorting the substance. When Purdue Pharma, the manufacturer of the opioid drug OxyContin, redesigned the drug to make it so it couldn't be crushed and snorted, Hepatitis C rates (as well as heroin overdoses) in states with high rates of nonmedical use skyrocketed as people turned to injectable opioids like heroin.[39] Cutting down on needle availability,

[39] Lev Facher, "Study Shows Purdue's Switch to 'abuse-Deterrent' OxyContin Helped Drive a Spike in Hepatitis C Infections," *Stat News*, February 4, 2019.

through measures like criminalizing ownership of paraphernalia, encourages reusing needles. Making sure supplies aren't accessible doesn't make people any less addicted.

In the United States, an average of 130 people die of opioid overdoses every day.[40] You've probably heard the words 'opioid epidemic', on the news or in casual conversation. Maybe you've seen the billboards (Fig. 1).

Figure 1: A billboard promoting medication safety outside Globe, Arizona.

Humans have been using derivatives of the opium poppy, or artificial mimics of the compound, for thousands of years. Opiates (the natural form of the drug) and opioids (the human-created versions) are powerful and effective drugs to manage pain. Unfortunately, they're also addictive. What we're calling "The Opioid Epidemic" is not even the first time that an artificial alternative to existing opiates or opioids has been falsely billed as non-addictive. Heroin, particularly after the American Civil War, was supposed to be a healthy alternative to morphine. It was even sold in cough syrups and calming elixirs for children. Unfortunately, it was just as addictive as the opiates it was supposed to replace.[41]

The current opioid epidemic started in the 1990s, when several drug companies found new formulations of opioids and marketed them aggressively, encouraging doctors to prescribe the medications and severely downplaying the risk patients might become

[40] Centers for Disease Control and Prevention, "Understanding the Epidemic | Drug Overdose | CDC Injury Center," December 19, 2018, https://www.cdc.gov/drugoverdose/epidemic/index.html.
[41] Macy, *Dopesick*.

addicted.[42] While it was by no means the only contributor to the problem, the drug that became the poster child of the epidemic was OxyContin, sold by Purdue Pharma LP.

OxyContin was supposed to offer long-acting relief and be difficult to abuse. The original version of OxyContin had been an end-of-life drug, a powerful painkiller meant for patients whose comfort in their last days far outweighed any risk of addiction.[43] Purdue adapted it for a wider audience. Like many other companies, it pushed pain itself as an indication something was seriously wrong, a symptom that *had* to be treated.[44] As a result of this massive marketing campaign, OxyContin was widely prescribed. To calm concerns about addiction, Purdue insisted OxyContin was difficult to abuse. The company also claimed that it was the individuals prone to misuse drugs who were the problem, rather than the drugs themselves.[45]

This was false. Oxy-Contin was addictive. And it was possible to abuse it. Patients coming off their short-term prescriptions after routine surgeries found themselves suffering withdrawal: shakes, pain, headaches, vomiting and diarrhea.[46] To avoid this misery, they turned to illegally obtaining prescriptions. Purdue's attempts to prevent abuse actually just made that abuse riskier. A reformulation of Oxy-Contin to ensure it couldn't be crushed and snorted drove users to heroin and other injectables instead.[47] Drugs that are injected make transmission of blood-to-blood infections likely,

---

[42] Macy.
[43] Macy.
[44] Faith Karimi, "The Maker of OxyContin Insists It's Not to Blame for the Opioid Epidemic," *CNN*, June 20, 2019, https://www.cnn.com/2019/06/20/health/purdue-pharma-david-sackler-vanity-fair/index.html; Macy, *Dopesick*.
[45] Macy, *Dopesick*.
[46] Macy.
[47] Facher, "Study Shows Purdue's Switch to 'abuse-Deterrent' OxyContin Helped Drive a Spike in Hepatitis C Infections."

due to contaminated needles.[48] This anti-abuse reformulation of OxyContin caused Hepatitis C rates to triple in the most heavily affected states, as people turned from the pills to injecting drugs.[49]

Since the 1990s, opioid abuse has skyrocketed nationwide, as have overdoses and injection-related diseases. With the opioid epidemic in full swing, the legal liability and finger-pointing began. Purdue is facing over 1,600 lawsuits. These suits come from all levels of government, as well as class action lawsuits and suits brought by private citizens.[50] The central argument these lawsuits make is that Purdue, and the Sacklers, the family that owns Purdue, engaged in a marketing strategy that sold large quantities of the addictive drug to patients, heedless of the risks. In an ongoing Massachusetts case, prosecutors claim to have traced more than 600 patients in that state alone who began on Oxy-Contin and later died of overdoses.[51] The state claims that Purdue intentionally produced misleading information about the addictiveness of Oxy-Contin.[52]

Purdue, in return, is claiming that it's only partially responsible for the opioid epidemic because its share in the market is small. It's true that Oxy-Contin only accounts for a fraction of opioid sales, but it is a particularly strong drug, and thus more likely to drive addiction.[53] Litigation in the Massachusetts case is ongoing. In an Oklahoma case,

---

[48] Facher.
[49] Facher.
[50] Laura Strickler, "Purdue Pharma Offers $10-12 Billion to Settle Opioid Claims," *NBC News*, August 27, 2019, https://www.nbcnews.com/news/us-news/purdue-pharma-offers-10-12-billion-settle-opioid-claims-n1046526.
[51] "Opioid Patient Worth $200,000 a Year to Purdue, State Says," *Bloomberg.Com*, August 2, 2019, https://www.bloomberg.com/news/articles/2019-08-02/sacklers-are-massachusetts-ag-s-opioid-scapegoat-lawyer-says.
[52] Jan Hoffman, "Purdue Pharma and Sacklers Reach $270 Million Settlement in Opioid Lawsuit," *The New York Times*, March 26, 2019, sec. Health, https://www.nytimes.com/2019/03/26/health/opioids-purdue-pharma-oklahoma.html.
[53] "Opioid Patient Worth $200,000 a Year to Purdue, State Says."

Purdue and its owners have agreed to a $270 million out of court settlement. It's the third settlement that Purdue has reached over its sales of Oxy-Contin, setting precedent for the 1,600 other cases.[54]

Forty-eight states have filed lawsuits against Purdue.[55] The company is now trying to declare bankruptcy, which would allow it to negotiate a settlement with all the plaintiffs rather than be liable for damages from all 1,600 cases.[56]

Despite Purdue's protests that it's being singled out, it's not alone. Insys Theraputics is also exploring filing for bankruptcy. Its best-known drug is Subsys, based on an opioid called fentanyl and meant for cancer patients. In May 2019, a federal court convicted its founder of essentially bribing physicians to prescribe Subsys to patients who didn't need it.[57] Again in Oklahoma, Johnson & Johnson was ordered to pay $572 million after the court found it liable for the state's opioid epidemic.[58] Johnson & Johnson marketed Duragesic and Nucynta. Like Purdue, the state of Oklahoma claims that Johnson & Johnson downplayed the addictive risks. Like Purdue, Johnson & Johnson is claiming that its drugs only account for a fraction of the opioid market.[59]

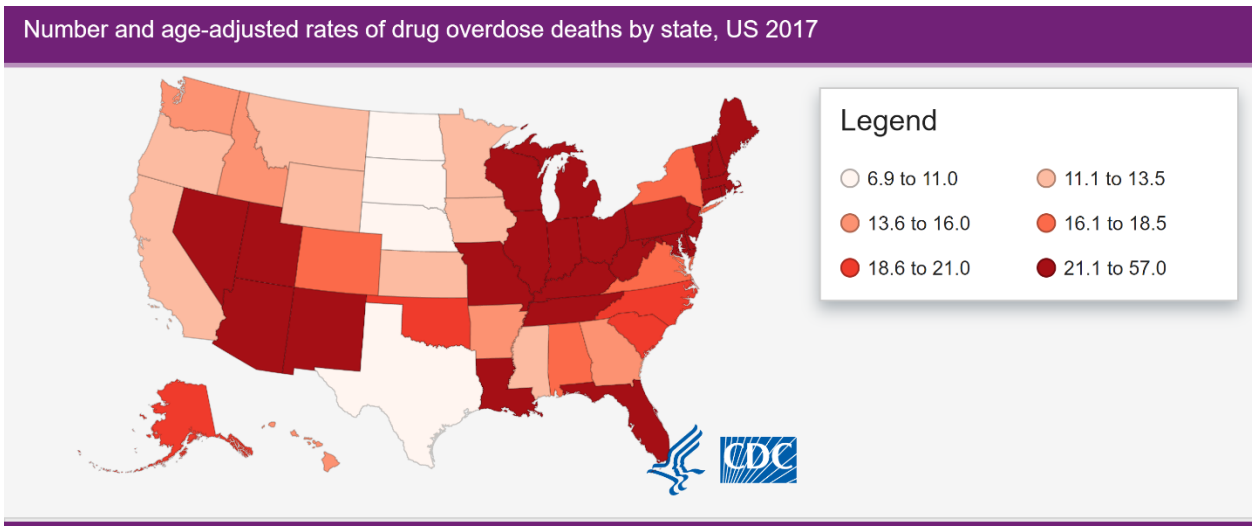
---

[54] Hoffman, "Purdue Pharma and Sacklers Reach $270 Million Settlement in Opioid Lawsuit."
[55] Berkeley Lovelace Jr., "Nearly Every US State Is Now Suing OxyContin Maker Purdue Pharma," *CNBC*, June 4, 2019, https://www.cnbc.com/2019/06/04/nearly-every-us-state-is-now-suing-oxycontin-maker-purdue-pharma.html.
[56] Mike Spector, Jessica DiNapoli, and Nate Raymond, "Exclusive: OxyContin Maker Purdue Pharma Exploring Bankruptcy -Sources," *Reuters*, March 5, 2019, https://www.reuters.com/article/uk-purduepharma-bankruptcy-exclusive-idUSKCN1QL1KP.
[57] Ashley Turner, "Drugmaker Insys Shares Tank after Saying Opioid Lawsuits May Force It into Bankruptcy," *CNBC*, May 13, 2019, https://www.cnbc.com/2019/05/13/insys-stock-tanks-after-saying-it-may-be-forced-to-file-bankruptcy.html.
[58] Jan Hoffman, "Johnson & Johnson Ordered to Pay $572 Million in Landmark Opioid Trial," *The New York Times*, August 26, 2019, sec. Health, https://www.nytimes.com/2019/08/26/health/oklahoma-opioids-johnson-and-johnson.html.
[59] Nate Raymond, "Oklahoma Judge to Rule on Monday in Opioid Lawsuit against J&J," *Reuters*, August 22, 2019, https://www.reuters.com/article/us-usa-opioids-litigation-oklahoma-idUSKCN1VB1TO.

These lawsuits are only the newest wave of litigation. In 2007, a federal criminal trial found Purdue and three of its executives guilty of misleading regulators and doctors—and by extension patients—about the risks of OxyContin. The company was fined $600 million, and three of its executives were also found guilty of misbranding the drug, paying another $34.5 million.[60]

Purdue's profits from opioids have dropped over the last few years. In 2012, profits from their opioids amounted to $2.6 billion. In 2017, they were $1.74 billion. The company now seems most interested in treatments for insomnia and cancer.[61]

The effects linger on. The CDC's 2019 report on opioid abuse estimated that 53 million Americans were misusing opioids.[62] Those who use injectable formulations of the drugs are at risk for Hepatitis C. And in 2017, 47,600 people died of opioid-related



overdoses.[63]

[60] Barry Meier, "In Guilty Plea, OxyContin Maker to Pay $600 Million," *The New York Times*, May 10, 2007, sec. Business Day, http://www.nytimes.com/2007/05/10/business/11drug-web.html.
[61] Spector, DiNapoli, and Raymond, "OxyContin Maker Purdue Pharma Exploring Bankruptcy."
[62] CDC National Center for Injury Prevention and Control, "2019 Annual Surveillance Report of Drug-Related Risks and Outcomes" (Atlanta, Georgia: Centers for Disease Control and Prevention, November 1, 2019), https://www.cdc.gov/ drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf.
[63] Spector, DiNapoli, and Raymond, "OxyContin Maker Purdue Pharma Exploring Bankruptcy."

Figure 2: Map of Drug Overdose Deaths in the United States, 2017.[64]

The map of opioid overdoses today is a pretty good predictor of what Hepatitis C statistics will look like in the next few years, if access to diagnosis and treatment isn't increased. Hepatitis C rides the coattails of the opioid epidemic. Even when the opioid epidemic is contained, Hepatitis C will linger in its footprints. Hepatitis C is hard to diagnose, expensive to treat. This combination will only make the eventual tide of illness worse; in order to prevent the worsening of the Hepatitis C epidemic, both of those barriers will have to be removed.

Opioid addiction itself isn't the only thing helping Hepatitis C spread. The structural violence that people who inject drugs face makes it both more likely this population will spread the disease, and makes it much more difficult for them to access treatment. A central link in the chain that gets PWID sick and keeps them sick is the criminalization of drug use. Twenty percent of people who report using illicit drugs also report having spent some time in prison.[65] A full third of Hepatitis C patients in the United States will spend some part of their lives in a jail or prison, often on drug-related charges.[66]

Laws that make it illegal to possess syringes or other drug paraphernalia decrease access to clean syringes and injection equipment, which increases transmission. HIV has

---

[64] Centers for Disease Control and Prevention, "2017 Drug Overdose Death Rates | Drug Overdose | CDC Injury Center," accessed March 15, 2020, https://www.cdc.gov/drugoverdose/data/statedeaths/drug-overdose-death-2017.html.
[65] Paul J. Joudrey et al., "A Conceptual Model for Understanding Post-Release Opioid-Related Overdose Risk," *Addiction Science & Clinical Practice* 14, no. 1 (April 15, 2019): 17, https://doi.org/10.1186/s13722-019-0145-5.
[66] Adam L. Beckman et al., "New Hepatitis C Drugs Are Very Costly And Unavailable To Many State Prisoners," *Health Affairs* 35, no. 10 (October 2016): 1893–1901, https://doi.org/10.1377/hlthaff.2016.0296.

similar risk factors. A study in Massachusetts showed that paraphernalia laws actively impede efforts to prevent HIV transmission.[67]

All these factors combine to keep Hepatitis C prevalence in prisons high. In New Mexico, about 43% of prisoners are Hepatitis C positive on intake.[68] In prisons, drug use is higher than it is in the rest of the country.[69] Even worse, it's a circumstance in which prisoners can't access the materials needed to inject safely. With a large number of prisoners already infected by Hepatitis C, this increases the risk of transmission significantly. Drug use isn't the only high-risk behavior that prisoners participate in or are exposed to. Violence and unprotected sexual encounters are also potential methods of transmission.[70] Furthermore, the longer someone is in prison, the more their risk for injection drug use or sexual activity increases.[71]

Because of employment and licensing restrictions placed on people with previous criminal convictions, Hepatitis C patients who have been imprisoned face severe economic hardship once they're released, making treatment even harder to access.[72]

---

[67] P. Case, T. Meehan, and T. S. Jones, "Arrests and Incarceration of Injection Drug Users for Syringe Possession in Massachusetts: Implications for HIV Prevention," *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology: Official Publication of the International Retrovirology Association* 18 Suppl 1 (1998): S71-75.

[68] K. Thornton et al., "FRI-186 - Treatment of Chronic Hepatitis C Virus (HCV) Infections with Direct Acting Antivirals in the New Mexico State Prison System Using the Project ECHO Model," *Journal of Hepatology*, Abstracts of The International Liver Congress 2017 — 52nd Annual meeting of the European Association for the Study of the Liver, 66, no. 1, Supplement (January 1, 2017): S492, https://doi.org/10.1016/S0168-8278(17)31380-6.

[69] Mary Jane Burton, Kathleen H. Reilly, and Alan Penman, "Incarceration as a Risk Factor for Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-Infection in Mississippi," *Journal of Health Care for the Poor and Underserved* 21, no. 4 (November 19, 2010): 1194–1202.

[70] Burton, Reilly, and Penman.

[71] Sandro Galea and David Vlahov, "Social Determinants and the Health of Drug Users: Socioeconomic Status, Homelessness, and Incarceration," *Public Health Reports (1974-)* 117 (2002): S135–45.

[72] Tracy Jan, "After Prison, a Lifetime of Economic Punishment," *Washington Post*, September 3, 2019, https://www.washingtonpost.com/graphics/2019/business/jobs-after-prison-rhode-island-recently-occupational-licensing/.

People very often return to drug use after they're released, and if they have spent time in prison not using drugs, their tolerances for the substance can be reduced. This means someone newly released may take an accustomed dose of an opioid and die from a resulting overdose. In fact, people newly released from prison have 129 times the risk of death from an overdose than the rest of the population.[73] Further, people released from prison after acquiring Hepatitis C in prison can continue transmitting the disease.

The association of Hepatitis C and drug use also confers a stigma on someone's Hepatitis C status. One former patient summed up this stigma: "I know about being, you know, made to feel shame about it. I know about being at the doctors office and saying 'I've had C,' and the question comes out, "So how'd you get that? Right? And what they're doing is setting up, *am I innocent or not?*"

This very stigma can keep people who inject drugs from seeking treatment at all. The harm reduction group I spoke with attributed this barrier to an internalization of the rest of society's opinions about injection drug use; the narrative about people who inject drugs is so pervasive that many of the group's patients feel that they're not worth saving and are reluctant to try to access treatment.

People who inject drugs ought to be on the front lines of those receiving treatment. They're at the highest risk, and if they do have Hepatitis C, they're in a prime position to spread it. Due to the difficulty of accessing treatment for drug use, (and the medical consequences of 'going cold turkey', which can be fatal), it's impractical to expect the average drug user to successfully recover and then seek Hepatitis C treatment,

[73] Joudrey et al., "A Conceptual Model for Understanding Post-Release Opioid-Related Overdose Risk."

as many state Medicaid access restrictions for Hepatitis C treatment stipulate.[74] It is not only the opioid epidemic driving the spread of the disease, but the consistent ostracization and criminalization of the most vulnerable to Hepatitis C.

[74] Macy, *Dopesick*.

CHAPTER 4

"WORSE THAN CHEMOTHERAPY"--THE EARLY HEPATITIS C TREATMENTS

The pressure to study and find a treatment for Hepatitis C in the 1990s was immense. One driving force was the nature of the treatments that offered the only hope for Hepatitis C patients. These treatments were small proteins called *interferons,* which are produced by animal cells as part of the body's immune response. Humans have seven different types of interferons, though only three are used clinically. Interferons have been used for treating conditions as different as cancer, varicella, herpes, and chickenpox. They work by making the immune system overreact, which stresses any invading microorganism as well as the host's body.[75]

It took a long time after the discovery of interferons before they were usable for treating diseases. Early samples were impure, and had very little interferon in them. It also turned out that interferons were species-specific, making it difficult to produce enough pure human interferon to do anything but test it on cells in culture.[76]

A breakthrough in the 1970s produced enough interferon to allow its testing in clinical settings. Initially, common viruses were the focus of interferon research, such as shingles, chickenpox, herpes, and the common cold. These studies didn't really go anywhere. Neither did the studies on interferon treatment of cancer. What did initially show promise, and continued to show promise, was the use of interferon to treat chronic hepatitis B infection.[77]

---

[75] Robert M. Friedman and Sara Contente, "Treatment of Hepatitis C Infections with Interferon: A Historical Perspective," *Hepatitis Research and Treatment* 2010 (2010), https://doi.org/10.1155/2010/323926.
[76] Friedman and Contente.
[77] Friedman and Contente.

Treating HBV patients with interferon seemed to cure a minority.[78] Though it was far from a universal cure, the fact that interferon was at all effective against Hepatitis B raised interest in its uses for treating Non-A-Non-B hepatitis (the virus wasn't isolated and identified for another decade or so after this research). A pilot study was conducted, with encouraging results. Larger trials followed. They, too, cured NANBH in a number of cases—enough to indicate it was worthwhile to continue research. The 1990s were a period of refining interferon treatment—how long, how to modify it.[79]

Combining interferon with ribavirin increased its effectiveness. We still don't know how exactly ribavirin works, but it does inhibit replication in RNA viruses. The other major advance was pegalyating the interferon—adding polyethylene glycol. This addition meant that interferon stayed in the body longer, so that patients didn't need to receive treatments as frequently.[80]

The final result was that between 30% (patients who fell into the least responsive groups) and 60% (patients in the most responsive groups) of patients receiving this treatment, known as combination therapy, achieved a sustained virological response, or SVR. This meant there were fewer virons attacking the human host's body. An actual cure, the elimination of the virus entirely, wasn't certain, and sometimes the disease returned.

---

[78] Ching-Lung Lai and Man-Fung Yuen, "Chronic Hepatitis B — New Goals, New Treatment," *New England Journal of Medicine* 359, no. 23 (December 4, 2008): 2488–91, https://doi.org/10.1056/NEJMe0808185.
[79] Doris B. Strader and Leonard B. Seeff, "A Brief History of the Treatment of Viral Hepatitis C," *Clinical Liver Disease* 1, no. 1 (February 1, 2012): 6–11, https://doi.org/10.1002/cld.1.
[80] Friedman and Contente, "Treatment of Hepatitis C Infections with Interferon."

Whether the disease returned depended on what strain of Hepatitis C infected the patient. As you may recall, an early problem with identifying Hepatitis C was its genetic diversity, which has led scientists to classify it into genotypes, the most common of which are Genotypes 1 through 4. Patients with different genotypes responded differently to therapy. Genotypes 2 and 3 were vulnerable. Genotype 1, the most common genotype causing disease in the United States, was not. Patients with it did not respond to interferon treatment. Neither did patients infected with Genotype 4.[81] Patients who had both HIV and Hepatitis C also had a very low chance of responding to treatment.[82]

Though interferon treatment offered a chance of a cure, it was hard on the patient. Early courses could last as long as a year—a year of interferon's vicious side effects for a 60% (at best) chance of recovery. "Without a doubt, it's one of the worst things that's ever happened to me," one recovered patient told me. "I was almost completely unable to function in society at all. I turned into somebody that I wasn't: mean, terrible thoughts, it was like mind control, about the world and everyone in it. It was something you'd have to endure every week. You would get the shot…I would literally just sit there and start crying."

Depression is a common side effect of interferon. So are flu-like symptoms. Another former patient described taking his shot just before bed, so he could sleep through the fever that it induced. He had to have three shots a week—one day of feeling sick, then feeling better the next day, rinse and repeat for a year. "It was absolutely

[81] Friedman and Contente.
[82] Tracy. Swan and HIV/AIDS Bureau., *Care and Treatment for Hepatitis C and HIV Coinfection: Expanding Access Though the Ryan White CARE Act* (Washington, D.C., UNITED STATES: United States Department of Health and Human Services, 2006), http://purl.access.gpo.gov/GPO/LPS77545.

atrocious to go through that therapy. You would have to give yourself the flu…You did that. You had to take three shots a week, and then there would be one day you'd have a break. That was the best day of the week. You felt almost normal that day. Then you'd have to take another. And you did that for 48 weeks."

The addition of ribavirin, while it made treatment far more effective, had its own side effects. It was mutagenic, causing malformations and mutations in sperm and eggs. "We had to put off having a family many years," that same former patient told me. But he stuck with the treatment. He'd already had a liver transplant, and had experienced the early stages of liver failure. "I was motivated. But if you had asked me to do that therapy five years earlier, when I felt normal, yeah right. There's no way."

Given interferon's myriad failings, a new kind of treatment was needed. The most feasible was a direct acting antiviral.

Direct acting antivirals have been around since the 1950s, but the progress in their development has been slow, especially compared to antibiotics, which treat bacteria.[83] Sofosbuvir and ledipasvir, two of the treatments for Hepatitis C, are a class of direct acting antiviral called *nucleoside analogues*. Nucleoside analogues are compounds that mimic the nucleotides that are the building blocks of RNA and DNA, in which viruses store their genetic information.[84] Nucleoside analogues are used to treat more than just viruses; some are used for cancer treatment, some for bacteria.

---

[83] O. L. Bryan-Marrugo et al., "History and Progress of Antiviral Drugs: From Acyclovir to Direct-Acting Antiviral Agents (DAAs) for Hepatitis C," *Medicina Universitaria* 17, no. 68 (July 1, 2015): 165–74, https://doi.org/10.1016/j.rmu.2015.05.003.

[84] Xueqiang Yin, "Mechanism Based Design and Synthesis of Nucleoside Analogues as Antiviral Agents" (Ph.D., United States -- Alabama, Auburn University, 2002), http://search.proquest.com/docview/304800333/abstract/5D8AAF60D73A4F9FPQ/1.

The way they work is by fooling the virus into using them as a building block for DNA or RNA, rather than the real nucleotide sequence that would allow the organism to reproduce. Since they're not the correct compound, the resulting genetic code doesn't work correctly. The new virus can't perform the functions it needs to perform to survive, or to replicate.

Some early nucleosides were actually intended as cancer treatments, such as 5-iodo-2-deoxyuridine (IDU). Invented by chemist William Prusoff, idoxuridine was intended to treat lymphoma.[85] Prusoff would later mentor Raymond Schinazi, the founder of Pharmasset, the company that created sofosbuvir, when both were at Harvard.[86] It turned out that IDU had much better results when treating herpes, though since it killed host cells as well, it was only used as a topical treatment. Today, it's sold as idoxuridine and used to treat herpes infections in the eye, which can rapidly progress and cause serious damage, including blindness. It has veterinary applications, too. My family has a cat who is on a daily dose of idoxuridine to control a chronic herpes infection in his eye, contracted when he was a kitten.

The major problem with idoxuridine is one shared by many of the early nucleoside analogues. The cellular damage it causes means it can't be ingested because it is taken up by human cells as well as viruses and bacteria. Many of its peers, nucleoside

[85] Maria C. Fioretti et al., "Immune Inhibition of Allogeneic Lymphoma Cells in the Peritoneal Cavity of Mice," *Cancer Research* 35, no. 1 (January 1, 1975): 30–36.
[86] Jon Cohen, "King of the Pills," *Science* 348, no. 6235 (May 8, 2015): 622–25, https://doi.org/10.1126/science.348.6235.622.

analogues discovered in the mid 1960s, are now discontinued because of their side effects.[87]

HIV treatments are the most well-known example of direct acting antivirals prior to Hepatitis C treatments. As with idoxuridine, these treatments had originally been developed for cancer treatment. The first of these compounds, suramin, worked on a low level against HIV, but it was quickly outpaced by a number of other compounds, including zidovudine (also known as AZT).[88] These compounds did slow disease progression, but had serious side effects. Another problem these drugs had to confront was that HIV replicates and mutates quickly, as many viruses that use RNA to encode their genomes do.[89] If treated with only one drug, HIV is very likely to rapidly develop resistance to that drug, and so the prescriptions of these drugs were only a stopgap for disease progression. The development of new compounds and the treatment of patients with a combination of them, however, was a successful strategy.

One of the researchers working on these drugs was Raymond Schinazi, who demonstrated anti-HIV activity in the antiretroviral D4T, and who played a significant role in the development of AZT as well. One of the early effective treatments for HIV, D4T is no longer recommended by US or international AIDS treatment bodies because of its toxicity, but is still used in low-income countries because of its affordability. Schinazi

---

[87] Katherine L. Seley-Radtke and Mary K. Yates, "The Evolution of Nucleoside Analogue Antivirals: A Review for Chemists and Non-Chemists. Part 1: Early Structural Modifications to the Nucleoside Scaffold," *Antiviral Research* 154 (June 2018): 66–86, https://doi.org/10.1016/j.antiviral.2018.04.004.
[88] John C. Martin et al., "Early Nucleoside Reverse Transcriptase Inhibitors for the Treatment of HIV: A Brief History of Stavudine (D4T) and Its Comparison with Other Dideoxynucleosides," *Antiviral Research*, Twenty-five Years of Antiretroviral Drug Development: Progress and Prospects, 85, no. 1 (January 1, 2010): 34–38, https://doi.org/10.1016/j.antiviral.2009.10.006.
[89] David Quammen, *Spillover : Animal Infections and the next Human Pandemic*, 1st ed.. (New York: W.W. Norton & Co., 2012).

went on to develop many other drugs for HIV—Emory University reports that about 94% of HIV patients worldwide have taken a drug that Schinazi was involved in developing.[90] He also founded several pharmaceutical companies, including Pharmasset.

Pharmasset, a small startup based in Atlanta, Georgia, would be the horse that won the race, the first company to produce a safe, effective drug for Hepatitis C. But before the virus could be inhibited, it had to be cultured, which proved to be a major challenge.

[90] Cohen, "King of the Pills."

CHAPTER 5

HOW TO CULTURE A VIRUS

Culturing Hepatitis C was a problem that had plagued researchers since the virus's discovery. They had a sequenced genome, but they couldn't grow it in a cell culture, only in living chimpanzees. Before any meaningful research could be done on ways to inhibit Hepatitis C, it had to be studied outside of the chimpanzee in carefully cultivated cells where treatments for the virus could be studied under controlled conditions. These conditions were also needed to better understand what the different parts of the virus's genome did, so researchers could identify which ones should be targeted by treatments, and which wouldn't yield any results. In order for it to be studied in cells, it had to be able to replicate in those cells. And getting Hepatitis C to replicate in culture was a remarkably difficult task.

The way in which the Hepatitis C virus was first identified was through a clone of the actual virus. Before anything else, that clone had to be complete and accurate. The first versions of it weren't. The initial clone was missing a significant piece of viral machinery, a piece of the 3' ('three-prime') end of its genetic sequence.[91] Without this, the clone of the virus couldn't replicate. And finding a way to stop a virus from replicating, when you can't get the virus to replicate in the first place, is pretty much impossible.

The first step was fixing the 3' end of the sequence. The clone had been thought to have the full 3' tail, but in 1995 and 1996, two research teams identified a sequence on the end of that tail that all Hepatitis C samples appeared to have, and that none of their

[91] Corinne L. Williams, "Ralf Bartenschlager, Charles Rice, and Michael Sofia Are Honored with the 2016 Lasker~DeBakey Clinical Medical Research Award," *The Journal of Clinical Investigation* 126, no. 10 (October 3, 2016): 3639–44, https://doi.org/10.1172/JCI90179.

cloned viruses had. Guessing that the lack of this sequence was responsible for the failure of replication in the previous Hepatitis C clones, they figured out a way to create a clone of the virus that included the vital sequence. They were successful, creating 10 clones that, when collectively injected into a pair of chimpanzees, caused the disease.[92]

But unfortunately, for both the researchers and the chimpanzees, what the clones still couldn't do was replicate in cell culture.

The Bartenschlager Laboratory at the Institute for Virology, Johannes-Gutenberg University was already working on Hepatitis C replication in culture. Ralf Bartenschlager had been educated at Heidelberg University, Germany, where he'd won an award for best PhD thesis from the Heidelberg Society for Molecular Biology. His work on Hepatitis C would gain him several other awards, including the prestigious Lasker-DeBakey Award, shared with Charles Rice and Michael Sofia in 2016.[93] One of the students in the Bartenschlager laboratory in the 1990s, Volker Lohmann, had attempted to create a cell culture system that could support Hepatitis C replication for his PhD thesis, but switched topics due to the difficulty of the project. After finishing the PhD in 1997, Lohmann returned to his research on a cell culture system, and in 1999, the work bore fruit. The result, a collaboration between researchers at the Institute for Virology, and Städtisches Klinikum Pforzheim (also in Germany) was a cell culture that could support Hepatitis C clone replication. This opened the door for the exact machinery of that replication to be studied and ultimately inhibited. [94]

---

[92] Williams.
[93] "CV_Ralf-Bartenschlager.Pdf," accessed July 22, 2019, https://www.dkfz.de/en/virus-assoziierte-karzinogenese/groups/AGBartenschlager/CV_Ralf-Bartenschlager.pdf?m=1487759647.
[94] Williams, "Ralf Bartenschlager, Charles Rice, and Michael Sofia Are Honored with the 2016 Lasker~DeBakey Clinical Medical Research Award."

The problem of getting Hepatitis C to replicate in culture was twofold. First, researchers needed a cell culture that would support the virus. Second, they needed a strain of the virus that was amenable to replicating in culture. The first of these goals was accomplished by Lohmann and Bartenschlager, after painstaking modification of a line of cells from a liver cancer patient to let the virus infect them more easily. They then marked these susceptible cells with a gene that gave them resistance to a drug that was usually toxic to cells. This allowed the researchers to select for only the cells that Hepatitis C could replicate in by poisoning the cell culture with this drug, and then using the surviving cells which had both resistance to the drug, and were prone to infection.[95]

The problem then arose that the modified versions of Hepatitis C that could replicate in this system couldn't replicate in a chimpanzee. The researchers had created a version of the virus that wasn't close enough to its unmodified relatives to work the way it did in a living organism. They needed a new strain that would work in culture and in living tissue.[96]

The breakthrough came in the form of a variety of Genotype 2 Hepatitis C virus isolated in a Japanese lab by Takaji Wakita and his colleagues. This strain, named JFH-1, could replicate in both cell culture and in living organisms. In 2005, three separate laboratories working independently managed to achieve consistent and complete replication of Hepatitis C in cell culture using this strain of virus. Bartenschlager would

[95] Williams.
[96] Williams.

later refer to the JFH-1 virus as "the jackpot",[97] the development that allowed immense progress in the treatment of Hepatitis C.[98]

The infective virus could now replicate in culture, and research on how to stop that replication could proceed. The horse race was on.

In order to understand how direct acting antivirals treat Hepatitis C, it's necessary to understand how the virus itself works. The virus's genome is a relatively short piece of RNA. The RNA is wrapped up with some proteins that together constitute the virus. Hepatitis C, like all other RNA and DNA sequences, reads from the 5' end to the 3' end. The 5' end is recognized by cellular machinery that begins the process of reading and replicating the RNA. It is followed by what are called 'structural proteins' that code for the nucleocapsid (a coat that surrounds the genome of the virus)[99], and the envelope glycoproteins, that work together to bind Hepatitis C to a host cell. This allows the virus to enter the host cell, and begin to hijack

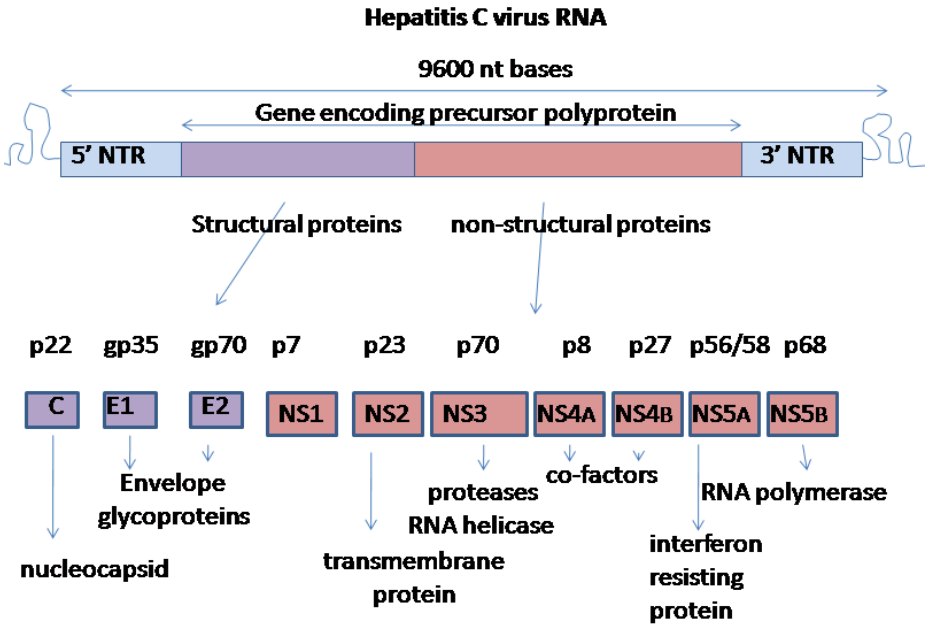


Figure 3: The genome of HCV. Credit: GrahamColm at English Wikipedia

[97] Williams.
[98] Williams.
[99] William Shiel, "Definition of Nucleocapsid," accessed July 24, 2019, https://www.medicinenet.com/script/main/art.asp?articlekey=24449.

the cell's own machinery to replicate.[100] Figure 3 shows the genome of the Hepatitis C virus, highlighting structural and nonstructural proteins and their roles in viral function.[101]

Structural proteins, while important for the virus's lifecycle, are not what this new generation of direct acting antivirals attack. They target the next parts of Hepatitis C 's genome, the nonstructural proteins, that code for the virus's replication.

Hepatitis C has seven nonstructural proteins. From the 5' end to the 3' end they are: p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B. p7 codes for an ion channel, which plays a wide variety of roles including the entry of the virus into the cell, regulating replication and assembly, and moderating electrochemical balance in the invaded cells.[102] So far, p7 hasn't been targeted by a direct acting antiviral. NS2 helps the virus get into the host cell, and it also codes for a cysteine protease, which is another of the virus's useful multitools, involved in diverse functions from protein folding to evading the host's immune system.[103]

With NS3 and NS4, we come to the nonstructural proteins that direct-acting antivirals target. Many of the earlier antivirals (boceprevir, telaprevir, and the still-extant simpervir) target the NS3/4 complex, which codes for a metalloprotease, which is partially responsible for the virus's replication. The next target is NS5A. NS5A is also

---

[100] Yimin Tong et al., "Role of Hepatitis C Virus Envelope Glycoprotein E1 in Virus Entry and Assembly," *Frontiers in Immunology* 9 (June 19, 2018), https://doi.org/10.3389/fimmu.2018.01411.
[101] "Hepatitis C Virus," in *Wikipedia*, July 11, 2020, https://en.wikipedia.org/w/index.php?title=Hepatitis_C_virus&oldid=967091076.
[102] Kai Wang, Shiqi Xie, and Bing Sun, "Viral Proteins Function as Ion Channels," *Biochimica et Biophysica Acta (BBA) - Biomembranes*, Viral Ion Channels, 1808, no. 2 (February 1, 2011): 510–15, https://doi.org/10.1016/j.bbamem.2010.05.006.
[103] Sonia Verma, Rajnikant Dixit, and Kailash C. Pandey, "Cysteine Proteases: Modes of Activation and Future Prospects as Pharmacological Targets," *Frontiers in Pharmacology* 7 (April 25, 2016), https://doi.org/10.3389/fphar.2016.00107.

involved with replication, and also codes for interferon resistance. One example of a DAA that attacks it is ledipasvir, a drug added to complement sofosbuvir in Gilead's second Hepatitis C drug, Harvoni, which allows Harvoni to be taken without a need for interferon.[104]

Sofosbuvir specifically targets the next gene down the road, the NS5B polymerase of Hepatitis C.[105] Figure 4 shows the replication process within the Hepatitis C virus, and how different direct acting antivirals interrupt it.[106]

Here's what we know about what the NS5B polymerase does: in DNA or RNA replication, it's the polymerase that does all the hard work. It stitches together the long string of nucleotides that make up RNA and DNA, thereby encoding the biological information they contain. When Hepatitis C is replicating, its RNA 'unzips', separating

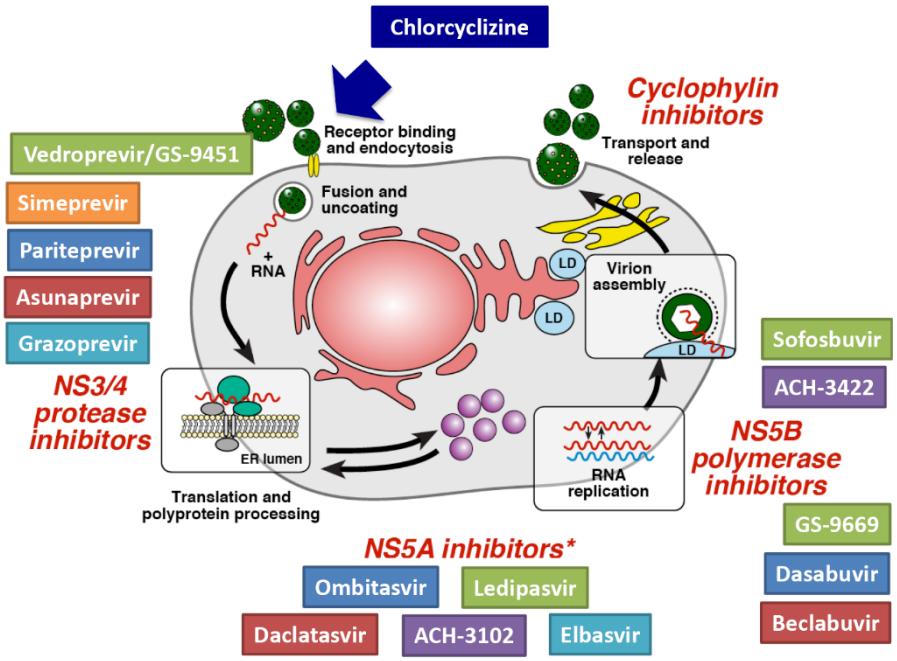


Figure 4: Viral replication and the stages at which direct acting antivirals stop replication. Credit: Poonia and Kottilil, 2016

[104] Anita Kohli et al., "Treatment of Hepatitis C: A Systematic Review," *JAMA* 312, no. 6 (August 13, 2014): 631–40, https://doi.org/10.1001/jama.2014.7085.
[105] Jeremy L. Clark et al., "Design, Synthesis, and Antiviral Activity of 2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication," *Journal of Medicinal Chemistry* 48, no. 17 (August 1, 2005): 5504–8, https://doi.org/10.1021/jm0502788.
[106] Bhawna Poonia and Shyam Kottilil, "Newer Therapeutics for Hepatitis C," *Annals of Translational Medicine* 4, no. 2 (January 2016), https://doi.org/10.3978/j.issn.2305-5839.2015.10.06.

into two separate, complementary strands. Each strand is the mirror of the other. Then, working from the 5' to the 3' end, polymerases 'read' the RNA strand and construct a new complementary strand for each, pulling in nucleotides from the surrounding cell. This creates two 'daughter' RNA strands from a single 'parent' strand.[107] The introduction of a nucleoside analogue throws a molecular wrench into this process. The polymerase will grab a nucleoside analogue that 'looks' like the real deal, but it will be defective. This will cause replication to fail. It's an effective way to stop a virus in its tracks. It demonstrates the necessity of carefully targeting a nucleoside analogue—because if a human polymerase picks it up, it can do the same thing and harm the host cells.

The problem faced by Hepatitis C researchers was twofold just as the problem faced in developing a cell culturing system. First, researchers had to locate and create compounds that would accurately mimic nucleotides well enough to get introduced into the virus in the first place, but they had to make these specific to Hepatitis C. If they did not, the drug would hurt the people taking it just as much as it would the virus.

[107] "DNA Polymerase - an Overview," Science Direct Topics, accessed July 19, 2019, https://www.sciencedirect.com/topics/neuroscience/dna-polymerase.

CHAPTER 6

THE MAKING OF MIRACLES--THE DEVELOPMENT OF SOFOSBUVIR

At Emory University, Raymond Schinazi and Dennis Liotta were working on just that: nucleoside analogues that wouldn't hurt the patient as much as the virus they aimed to destroy. Their earliest patents on the forerunners of sofosbuvir dated from the mid-1990s.[108]

This ancestor of sofosbuvir was a nucleoside that had been modified by the introduction of a fluorine atom instead of hydrogen. A fluoro-group molecule is a molecule that contains a compound based on fluorine, a highly reactive element that, in medicinal chemistry, can modify a compound to become more biologically and chemically stable. It is much harder to break a fluorine bond than one to hydrogen. The bond between the fluoro-group and the rest of the structure closely mimics the structure of a normal nucleotide, which means that it's likely to fool a polymerase into picking it up instead of a real nucleotide.[109]

Originally, Schinazi and Liotta were investigating fluorinated nucleosides as a treatment for HIV and Hepatitis B.[110] By 1999, they'd found a compound they were investigating for use against Hepatitis C, as well.[111]

---

[108] Raymond F. Schinazi and Dennis C. Liotta, Compositions containing 5-fluoro-2',3'-didehydro-2',3'-dideoxycytidine or a mono-, di-, or triphosphate thereof and a second antiviral agent, United States US5703058A, filed January 27, 1995, and issued December 30, 1997, https://patents.google.com/patent/US5703058A/en; Raymond F. Schinazi et al., 2′-Fluoronucleosides, United States US7307065B2, filed March 8, 2004, and issued December 11, 2007, https://patents.google.com/patent/US7307065/en?oq=schnazi+patent+fluoro+nucleosides+1999.
[109] Peng Liu, Ashoke Sharon, and Chung K Chu, "Fluorinated Nucleosides: Synthesis and Biological Implication," *Journal of Fluorine Chemistry* 129, no. 9 (September 2008): 743–66, https://doi.org/10.1016/j.jfluchem.2008.06.007.
[110] Schinazi and Liotta, Compositions containing 5-fluoro-2',3'-didehydro-2',3'-dideoxycytidine or a mono-, di-, or triphosphate thereof and a second antiviral agent.
[111] Raymond F. Schinazi et al., 2′-Fluoronucleosides, United States, filed February 25, 1999, and issued February 19, 2002, https://patents.google.com/patent/US6348587B1/en.

Pharmasset was founded in 1998, out of frustration. Schinazi strongly felt that the prodrugs he researched weren't receiving attention or funding in the academic or public realm—he had a dual appointment at Emory and the Department of Veterans' Affairs at that point, so he and Dennis Liotta gave the private sector a try, founding Pharmasset and a sister company, Idenix, in the same year.[112] There, they looked into a different type of nucleoside, one that had a structure made of oxygen, hydrogen, and a methyl group to treat the various viral diseases.[113]

Around this time, Merck became interested in a collaboration with Pharmasset. It, too, was working on nucleoside analogue drugs specifically for Hepatitis C, and it was interested in the work that Pharmasset was doing in the area. It had a 2002 patent on a nucleoside derivative intended to treat RNA virus infection.[114] A Pharmasset chemist, Jeremy Clark, reviewed the patent application and proposed a fluorinated nucleoside, PSI-6130. The first paper on this drug was published in 2005. It described two fluorinated nucleosides that acted on the NS5B polymerase of Hepatitis C. One of the two compounds was promising. It seemed to inhibit the virus but didn't affect the host cells at all.[115] PSI-6130 became the lead compound for sofosbuvir. Lead compounds are promising compounds that have some potential to become a useful drug, but still require refinement to become a safe and effective drug in humans.

---

[112] Interview with HCV Researcher, n.d.
[113] Kyoichi A. Watanabe and Balakrishna S. Pai, 3'-or 2'-hydroxymethyl substituted nucleoside derivatives for treatment of hepatitis virus infections, World Intellectual Property Organization WO2001079246A2, filed April 13, 2001, and issued October 25, 2001, https://patents.google.com/patent/WO2001079246A2/en.
[114] Steven S. Carroll et al., Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase, United States US7105499B2, filed January 18, 2002, and issued September 12, 2006, https://patents.google.com/patent/US7105499B2/en.
[115] Clark et al., "Design, Synthesis, and Antiviral Activity of 2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication."

Shortly after that publication, Jeremy Clark left Pharmasset for the Southern Research Institute in Georgia, leaving the intellectual property rights for PSI-6130 with his former employer, Pharmasset, as per the contract he had signed. Work on PSI-6130 continued without him. An independent laboratory confirmed Pharmasset's findings that the compound was both effective against Hepatitis C and not toxic to cells.[116]

The California laboratory confirming this was attached to the Swiss company Roche. At this point, Roche and Pharmasset were collaborating on research for Hepatitis C treatment development.[117] But there were still some issues with the drug to work out.

It was at this point that Michael Sofia, the scientist for whom sofosbuvir is named, entered the story.

Sofia had been working in the infectious disease realm for years, and was particularly interested in antivirals. He'd been involved in a Hepatitis C program at Bristol Meyers Squibb, and when he was recruited to Pharmasset, at the time a company whose research focused on HIV, he became interested in the Hepatitis C research the company was doing as well. The team working on the drug—the promising PSI-6130—was a small one, but the drug looked both capable of attacking Hepatitis C regardless of genotype, and safe. Where it really shone, however, was when it was combined with other DAAs in production. But it wasn't very potent, and patients had to take massive quantities of it, which meant it had to be refined.[118]

---

[116] Han Ma et al., "Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor β-d-2′-Deoxy-2′-Fluoro-2′-C-Methylcytidine (PSI-6130) and Identification of a Novel Active 5′-Triphosphate Species," *Journal of Biological Chemistry* 282, no. 41 (October 12, 2007): 29812–20, https://doi.org/10.1074/jbc.M705274200.
[117] "Pharmasset Nominates PSI-7851 as a Lead Development Candidate for the Treatment of Chronic Hepatitis C," accessed August 2, 2019, http://www.natap.org/2008/HCV/051908_02.htm.
[118] Interview with HCV Researcher.

Refinement meant knocking off all the parts of the drug that weren't doing patients any good. The particular problem was an inactive metabolite, which was a compound that was created when the body processed PSI-6130 that didn't do anything. A new drug was produced this way, in collaboration with Roche, and as it moved steadily through clinical trials, Sofia's attention landed back on PSI 6130. The Roche compound could treat Hepatitis C, but it wasn't ideal. Sofia suspected that another drug from PSI 6130 could do better.[119]

The problem was, when you phosphorylated PSI 6130, you got something that could linger in the body a long time (exactly what was needed to make an effective medication) but that did absolutely nothing to the virus. This drug, PSI 2606, was totally inert, because as a highly charged monophosphate, it couldn't get through cell walls. It could be metabolized into a triphosphate that *would* attack the virus, but first, it needed to get into a cell. But its inability to penetrate a cell membrane meant it couldn't do that.[120]

All cells have membranes, a layer made out of lipids, or fats (plants have membranes, but have an outer layer called a cell wall, that lends them rigidity; animals, including humans just have the membrane). If a compound is membrane impermeable, it means that it cannot get past this layer, a major impediment to a compound that is supposed to stop a virus replicating within a host cell.

Michael Sofia's contribution to the creation of sofosbuvir was fixing this problem. He called his solution a 'Trojan Horse'. This Trojan Horse was a coating of a material that *could* get through a cell membrane that encased and hid the nucleoside, allowing it to

[119] Interview with HCV Researcher.
[120] Interview with HCV Researcher.

sneak in. Once it was inside, the coating broke down, and the machinery of the cell processed the nucleoside into a nucleotide, allowing it to resemble the nucleotides the Hepatitis C virus used to replicate itself. But they weren't real nucleotides; rather, they were clever poisonous fakes, and they halted that viral replication in its tracks.

There was another clever thing about the design of sofosbuvir. When you digest something, it travels to your stomach, where it is broken down. Then it continues through your intestines, some 20 odd feet in which the molecules of the food that you need to live, or, the molecules of any medication you've taken, get absorbed into the bloodstream.

The blood with its cargo then travels to the liver. With a healthy liver, you don't need to do 'detox' diets or other activities to get rid of the toxins in your body. That's the liver's job. The blood travels into the liver, where the liver cleans it of any potential poisons, and then the blood with its nutrients continues on its way to the other parts of your body.

Sofia and the Pharmasset researchers decided to use this process (called 'first pass metabolism') to their advantage. Hepatitis C concentrates in the liver. So, if ingested, the medication should concentrate in the liver, conveniently targeting the area where it was most needed. Once the drug got into a cell, the phosphoramadate coating that had fooled the cell into letting it in came off. It got processed into the effective version of the drug. And since this was highly charged, it didn't exit the cell again. It stayed in the liver, where the most Hepatitis C virus was.[121]

This type of targeted delivery had never been done in a patient before. It was a risky business proposition, especially since Pharmasset and Roche were working on

[121] Interview with HCV Researcher.

another, similar drug. But the idea of sending the drug to the place where it was most needed, and *only* there, was too seductive. Sofia's team started working on making this invention a reality, testing vast numbers of molecules with new molecular techniques aimed to quickly assess the efficacy of vast numbers of candidate drugs against Hepatitis C at once.[122]

These modifications to PSI-6130 earned it a new name: PSI-7851, which was significantly more potent than the other Hepatitis C treatment that Pharmasset was working to develop with Roche.[123] In 2009, phase 1 clinical trials with this new molecule began in humans.

A Phase 1 clinical trial isn't primarily concerned with whether the drug cures the disease, but with whether the drug is safe for humans. Nucleoside analogues had a bad reputation for safety—remember how toxic idoxuridine is if ingested, and how that means it can only be used on the directly-infected eye, rather than taken systemically. But nucleoside analogues had come a long way since idoxuridine and the early HIV antiretrovirals like AZT. PSI-7851 caused no damage, referred to in clinical trials as 'adverse effects', to the patients who took it—and all the patients' viral loads decreased significantly.[124]

---

[122] Interview with HCV Researcher.
[123] "Pharmasset Nominates PSI-7851 as a Lead Development Candidate for the Treatment of Chronic Hepatitis C."
[124] "New HCV Nucleotide Polymerase PSI-7851 Achieves 1 Log Reduction in Viral Load in 3-Day Study," 2009, http://www.natap.org/2009/HCV/080109_01.htm; Angela M. Lam et al., "PSI-7851, a Pronucleotide of β-d-2′-Deoxy-2′-Fluoro-2′-C-Methyluridine Monophosphate, Is a Potent and Pan-Genotype Inhibitor of Hepatitis C Virus Replication," *Antimicrobial Agents and Chemotherapy* 54, no. 8 (August 1, 2010): 3187–96, https://doi.org/10.1128/AAC.00399-10; "Pharmasset Nominates PSI-7851 as a Lead Development Candidate for the Treatment of Chronic Hepatitis C."

Further study showed that PSI-7851was actually a mixture of two compounds, PSI-7976 and PSI-7977. PSI-7977 had the same formula as PSI-7976, but the arrangement of the atoms in the molecule mean that they had different three-dimensional structures. This is what's called a stereoisomerism in chemistry; specifically, PSI-7976 and PSI-7977 were mirror images of one another, meaning that the two compounds were *not* mere substitutes, but rather two distinct compounds. It turned out that, of the two, PSI-7977 was the most effective in inhibiting Hepatitis C.[125] Ten times more effective, one researcher told me.[126]

PSI-7977 was announced to the world in the Journal of Medicinal Chemistry in 2010. The line-up of researchers had changed over the years. Michael J. Otto and Phillip A. Furman, present on some of the earliest patents for fluorinated nucleoside analogues, remained. Schinazi and Liotta were absent. After Pharmasset moved its headquarters from Atlanta to Princeton, New Jersey in 2005, Schinazi had stepped down from a leadership position in 2006, retaining a 4% stake in the company.[127]

A year later, Pharmasset began talks with Gilead Sciences, leading to Gilead's much-publicized 11-billion-dollar acquisition of Pharmasset, and the renaming of PSI-7977 one more time into GS-7977.

PSI-7851 had passed Phase I clinical trials, demonstrating that it was safe in humans. It moved into Phase II equally smoothly, and PSI-7977 went into Phase III

---

[125] Eisuke Murakami et al., "Mechanism of Activation of PSI-7851 and Its Diastereoisomer PSI-7977," *Journal of Biological Chemistry* 285, no. 45 (November 5, 2010): 34337–47, https://doi.org/10.1074/jbc.M110.161802.
[126] Interview with HCV Researcher.
[127] "Gilead Could Have Had Pharmasset Cheap: Founder," *Reuters*, November 22, 2011, https://www.reuters.com/article/us-pharmasset-founder/gilead-could-have-had-pharmasset-cheap-founder-idUSTRE7AL2ES20111122; Erin Moriarty, "Scientist Forms New Firm," *Atlanta Business Chronicle*, August 8, 2005, https://www.bizjournals.com/atlanta/stories/2005/08/08/story1.html.

clinical trials. Here it was tested in combination with a variety of other compounds, including others from Pharmasset, and the traditional combination therapy. Some of these trials were discontinued, always because of the other compounds. PSI 7977 remained effective and safe. It needed to be combined with interferon to be effective, but the course of treatment was much shorter, and it dispensed with the need for ribavirin.[128]

The process of clinical trials continued as Pharmasset was bought by Gilead. The results of the clinical trials showed that PSI-7977 (now GS-7977) was an effective treatment when given in combination with interferon and ribavirin. It was approved by the FDA in December of 2013. Its generic name was sofosbuvir. Its brand name, Sovaldi®.

[128] Eddie Staley, "Pharmasset Announces Intent to Amend QUANTUM Trial," *Business Insights: Global*, January 16, 2011, Fhttp://bi.galegroup.com.ezproxy1.lib.asu.edu/global/article/GALE%7CA275049166/adc42e0c1e4f179cb9d2482d538a82f3?u=asuniv.

CHAPTER 7

THE BUSINESS OF MIRACLES

Sofosbuvir (then known as PSI-7977) wasn't the only direct acting antiviral in development between 2008 and 2011. Telaprivir, owned by Vertex Pharmaceuticals, and boceprevir, owned by Merck, both made it to market in 2011 well before sofosbuvir did.[129] Both needed to be paired with interferon, and both had serious health side effects—but doctors and patients welcomed them anyway, since their success rates were so much better than simple combination therapy.[130] But a direct acting antiviral that didn't need to be paired with interferon? That was the holy grail, the subject of the horse race every company was competing in, and sofosbuvir looked to be the winning horse.

Pharmasset's clinical trials showed PSI-7977 nosing ahead, a drug that was not only extremely effective, but also remarkably safe. Internal documents from Pharmasset showed researchers and executives were well aware of this. PSI-7977 was "less risky than other drugs at this stage of development".[131]

Pharmaceutical companies took notice. Soon, Pharmasset started getting offers to acquire it. Pharmasset hired financial advisors.

---

[129] Vertex Pharmaceuticals Incorporated, "FDA Approves INCIVEK™ (Telaprevir) for People with Hepatitis C," Vertex Pharmaceuticals, May 23, 2011, https://investors.vrtx.com/news-releases/news-release-details/fda-approves-incivektm-telaprevir-people-hepatitis-c; Merck, "Merck Press Release: FDA Approves Merck's VICTRELIS (Boceprevir), First-in-Class Oral Hepatitis C Virus (HCV) Protease Inhibitor," accessed September 30, 2019, http://www.natap.org/2011/HCV/051811_05.htm.

[130] Christophe Hézode et al., "Telaprevir and Peginterferon with or without Ribavirin for Chronic HCV Infection," *New England Journal of Medicine* 360, no. 18 (April 30, 2009): 1839–50, https://doi.org/10.1056/NEJMoa0807650; Charles Johnson and Vertex Pharmaceuticals Incorporated, "Discontinuation of INCIVEK® (Telaprevir) Tablets in the United States," August 11, 2014, http://freepdfhosting.com/f75f8bac14.pdf.

[131] "The Price of Sovaldi and Its Impact on the United States Health Care System," § COMMITTEE ON FINANCE UNITED STATES SENATE (2015), https://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20(Full%20Report).pdf.

One of the companies making an offer was Gilead Sciences. Gilead was founded in 1987 as "Oligogen", and changed its name to "Gilead Sciences" the next year. Its first drugs treated a variety of conditions, including many secondary infections in HIV+ or immunocompromised patients. It then moved its focus to antivirals. Tamiflu, the drug stockpiled against bird flu, is a Gilead product. But, prior to the release of sofosbuvir, it was best known for its HIV antiretroviral drugs.[132]

Notable among those antiretrovirals was emtricitabine, sold as Emtriva, a treatment for HIV. This was acquired by the buyout of Triangle Pharmaceuticals, a start-up founded by Raymond Schinazi, who also founded Pharmasset.[133]

Gilead's own efforts to develop a Hepatitis C drug hadn't been successful. By 2011, it decided that acquiring Pharmasset and PSI-7977 was its best, and possibly its only, bet for getting into the Hep C market. Time was an issue. It was unlikely Pharmasset would still be available for acquisition in the next year. PSI-7977 was too promising, and it was too likely someone else would snap it up, closing Gilead out of the potentially profitable Hep C market.[134]

After all, Hep C was a vastly undertreated epidemic. If a drug like sofosbuvir could be brought to market, if it could be turned into a regimen that didn't need interferon and its punishing side-effects, then whomever had done that bringing would have millions of desperate potential customers.

---

[132] "Corporate History Timeline | Gilead," accessed April 3, 2019, https://www.gilead.com/about/corporate-history; "History of Gilead Sciences, Inc. – FundingUniverse," accessed April 3, 2019, http://www.fundinguniverse.com/company-histories/gilead-sciences-inc-history/.
[133] "Gilead Sciences - SourceWatch," accessed April 3, 2019, https://www.sourcewatch.org/index.php/Gilead_Sciences; Gilead, "Gilead Sciences to Acquire Triangle Pharmaceuticals for $464 Million | Gilead," December 4, 2002, https://www.gilead.com/news/press-releases/2002/12/gilead-sciences-to-acquire-triangle-pharmaceuticals-for-464-million.
[134] The Price of Sovaldi and its Impact on the United States Health Care System.

And PSI-7977 looked *good.* It was simple, a single pill daily, taken in combination with a shorter course of interferon. Its clinical trials were having good luck recruiting patients. It was far along in its development process.

Meanwhile, Gilead's own Hepatitis C drugs weren't doing well. Patients in clinical trials were experiencing adverse effects. Gilead didn't have time to start from scratch. The field was too packed, and there were too many other candidate drugs in development.

Acquiring Pharmasset was the logical way forward. Using code names ("Harry" for Pharmasset, "Gryffindor" for Gilead—a nod to the immensely popular Harry Potter books), Gilead planned the acquisition. Pharmasset provided them with confidential information about its research and finances, and the team tasked with reviewing them liked what they found.[135]

Encouraged by these findings, Gilead increased its initial offer to the final price of $11.2 billion. Pharmasset took it. Two weeks before the acquisition was announced, Pharmasset released the results from its most recent clinical trial. In this trial, PSI-7977 cured *every single patient in the treatment groups.*[136]

But even these immensely promising results didn't soothe investors. Gilead had just made a very expensive, risky gamble, and the investors were worried. The announcement of the acquisition triggered a sell-off of Gilead's stock, causing its value to fall. Now that Gilead had made its bet, it had to ensure its horse would pay.

Originally, Pharmasset had planned to sell sofosbuvir for much cheaper than the final pricing, about $36000 per 12-week course of treatment. Some documents indicated

[135] The Price of Sovaldi and its Impact on the United States Health Care System.
[136] The Price of Sovaldi and its Impact on the United States Health Care System.

that Pharmasset was looking at a higher price point, (about $72000) inspired by Incivek, the DAA sold by Vertex. However, the documents quoting higher potential prices were from the later part of the acquisition process, when it was in Pharmasset's best interest to make its product as valuable as possible.

That $72000 multiplied by the number of patients Gilead could reasonably expect to treat would have paid Gilead $2 for every $1 they'd spent on acquiring Pharmasset. That Pharmasset didn't ask for more money shows that it probably didn't take that higher price point very seriously.

But Gilead would.

At first, Gilead's expectations were relatively modest. It was considering between $55000 to $75000 per course of treatment. This would be the price before discounts were given to payers, and, of course, American patients would be charged a premium compared to patients in Europe and Japan. Drug prices are commonly higher in the United States than they are abroad for a variety of reasons, chief among them being that a unified health system allows a country significantly more bargaining power to set what prices it will pay for a drug than the fractured health system like that of the United States.[137]

Meanwhile, Gilead was benefiting from other US policies, thanks to Breakthrough Therapy Designation. This meant that Gilead was working on a drug that had the potential to save lives, and accordingly, the FDA applied policies that allowed its

[137] Sarah Kliff, "The True Story of America's Sky-High Prescription Drug Prices," *Vox*, November 30, 2016, https://www.vox.com/science-and-health/2016/11/30/12945756/prescription-drug-prices-explained; Judith L. Wagner and Elizabeth McCarthy, "International Differences in Drug Prices," *Annual Review of Public Health* 25, no. 1 (2004): 475–95, https://doi.org/10.1146/annurev.publhealth.25.101802.123042.

approval process to be significantly accelerated. This meant that sofosbuvir came to market much faster than its peers, and meant that it had the market more or less to itself for over a year, significantly bolstering its eventual profits. In 2014, the approval of Harvoni, a combination of sofosbuvir and ledipasvir that did away with the need for interferon to treat Hepatitis C, the second of Gilead's Hepatitis C treatments, would enjoy this status as well.

R&D costs to Gilead during the period between the acquisition of Pharmasset and the approval of Harvoni are unknown. A later congressional inquiry, started because of the outcome of Gilead's pricing decisions, requested them, but Gilead declined to provide them.

The Phase 3 clinical trials for sofosbuvir looked good. Technically (according to Gilead's policies, common in the industry), a pricing process should be based on how well the drug works, the cost of other, similar products on the market, what payers such as insurance companies can and are willing to pay, or already pay for similar products, and the determination of the product's value. The determination of a product's value is a complex process. It can consider the value generated by the product to the business, or that generated for the consumer, or its fit in the market (Is it unique? Are there other products like it?).[138]

In November 2012, Gilead was considering prices between $58,000 and $65,000, and planning on a 25% discount to patients in European countries where drug prices are more strictly regulated. A major factor was when, not if, competing products would hit

[138] Riche Zamor, “Measuring the Value of Your Product,” Phase2, April 16, 2017, https://www.phase2technology.com/blog/measuring-value-your.

the market, cutting into Gilead's profit margins as payers elected to use the new products. This made pushing the initial price point higher a good idea, at least until those competing products arrived.

Boceprevir and telaprevir were both already on the market, but they weren't nearly as effective as sofosbuvir promised to be, and they both needed interferon. Telaprivir could cost $55,273 for a 48-week course of treatment.[139]

In light of this, Gilead thought it might even be able to charge $121,000 per course of treatment, especially as its competitors drew closer to launching their own treatments. AbbVie, another pharmaceutical company, was developing its own all oral, no interferon regimen, which it called the Viekira Pak. Gilead would have to set the right stage for an all-oral regimen of their own (Harvoni, where sofosbuvir and ledipasvir were combined, then in development) to succeed, or lose that advantage. Sofosbuvir, being launched as Sovaldi, would have to be priced in such a way as to allow Harvoni's success…and Harvoni would have to be ready in time. But the Viekira Pak required a patient to take a lot of pills every day. Harvoni would only be a one-pill-a-day regimen. Gilead could charge for that convenience.

The one other product that showed similar promise, simeprevir, was not performing at the levels that sofosbuvir was, so the threat of its competition was much lower. Gilead could get away with pricing sofosbuvir that much more highly.

As powerful an argument as all this was for high prices, Gilead had to consider other factors, like how payers and activists might react to the prices it was considering.

---

[139] Miriam Tucker, "Costs for Hepatitis C Treatment Skyrocket," *Medscape*, November 3, 2013, http://www.medscape.com/viewarticle/814295.

One major issue was that a certain group of patients would need not one, but two, courses of treatment.

In most patient populations, specifically those with Genotype 1a (recall that a hallmark of Hepatitis C is its immense genetic diversity), sofosbuvir was incredibly effective. But in Genotypes 2 and 3, sofosbuvir didn't attain the same incredible sustained viral response rates it did in other populations. Sustained viral response refers to a consistent lack of detectable virus in the patient's blood. These patients could require 24 weeks of treatment, not just 12. And these patients, if sofosbuvir launched at a price that met the lofty aspirations of the pricing committee at Gilead, would end up paying twice the price of their counterparts with Genotype 1.[140]

Gilead's concern regarding these patients was how to keep that part of the story from "dominat[ing] the narrative at launch".[141] Surely, with the demonstrated efficacy of sofosbuvir, payers would be willing to pony up to cure these patients too.

Another issue at hand was the Affordable Care Act. The Affordable Care Act had expanded Medicaid and Medicare. This meant that two large public payer systems were responsible for more people than ever. Many of those people might have Hep C and need treatment. There might be a strain on the system that would impede paying, simply because of the number of people who might need the treatment. This, in turn, could lead to outside pressure on Gilead to lower its prices.

Accordingly, sofosbuvir's price point was revised down to between $80,000 and $90,000. Gilead researched payer willingness to pay these prices. Payers seemed

[140] The Price of Sovaldi and its Impact on the United States Health Care System.
[141] The Price of Sovaldi and its Impact on the United States Health Care System.

interested, but concerned about expense, especially Medicaid payers. But still Gilead focused on that price point of $80,000-$90,000. It would maximize profit while keeping the price low enough to avoid an outcry.

Or so Gilead thought, despite the advice and emails that poured in from experts, warning of the fears of payers about the immediate costs of the drugs, leaving vulnerable populations out in the cold.[142] One email from the Fair Pricing Commission, a group that Gilead itself had funded, began:

> "We should remind you of our original warning that, even though new DAAs are a major improvement that may be cost-effective in the long run, our healthcare system lacks this particular downstream thinking. Both government and industry payer programs operate under short-term budget constraints that are incapable of absorbing the costs of Sovaldi for every patient they cover who needs access to this medication."[143]

To say this was a prescient statement isn't appropriate. It was a logical statement, no clairvoyance required, to anyone familiar with the United States healthcare system. But Gilead didn't significantly lower the price. It used the same pricing process on Harvoni, bolstered by the success of sofosbuvir. Its anticipated launch price was $94,500 for a 12-week course of treatment.

This price was made possible by the pricing of sofosbuvir. Again, Gilead consulted payers, ranking them by importance to their market. On the first tier were private health insurers and Medicare, deemed the most important potential customers. Medicaid was only assigned middling importance. Departments of Correction were given a similar ranking. Indeed, Gilead decided that only the Departments of Correction of five states should receive discounts. Other states weren't deemed profitable enough, despite

[142] The Price of Sovaldi and its Impact on the United States Health Care System.
[143] The Price of Sovaldi and its Impact on the United States Health Care System.

Hepatitis C infection in the prison population being significantly higher than that in the general population—between 16%-41%, versus about 1% for the general population.[144]

The effects on those payers in the low and middle tiers were profound. States had difficulty accessing rebates that were sufficient to make the drug accessible. This meant that states simply could not afford enough of the drugs to treat patients, leading to treatment restrictions and rationing.

Though Gilead had attributed significant importance to the US Department of Veterans Affairs as a payer, putting it on the top tier of potential customers, it, too, struggled to provide treatment to people under its care.

These decisions by Gilead weren't sustainable decisions from a public health standpoint. They were, however, reasonable from the point of view of a business. Pharmaceutical businesses have some specific motivations that strongly encourage thinking like this.

Chief among these motivations is the securing of patents, which are more or less government-protected monopolies on new drugs. Since these drugs can make the difference between life or death for patients, or at least the alleviation of misery, it's been easy for companies holding these patents to charge high prices, citing the patient's necessity and the cost of development as justification. Many of the pharmaceutical researchers I spoke to gave me just this justification for sofosbuvir's price. The rewards of holding a patent, of being the only company allowed to make and sell a cure, can be immense. Until a patent expires, generally 20 years after the date of filing an

[144] American Association for the Study of Liver Diseases and Infectious Diseases Society of America, "HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C," May 24, 2018, https://www.hcvguidelines.org/unique-populations/correctional.

application,[145] and generic drugs can take the market, all you have to do is worry about competing products from other companies that are different but aimed at treating the same illness. This means there's substantial time pressure to maximize your profits before your competitors show up. It also adds a motivation to participate in what's called "evergreening" of patents, where a company changes an invention just enough to get a new patent on it, so they can continue to enjoy the protections patents enjoy.

Furthermore, this system rewards buying smaller companies over doing your own research. The only thing that made Gilead's purchase of Pharmasset unusual was the hefty price. The industry rewards massive short-term profits more than lower long-term profits. It is easier to earn short-term profits by buying up smaller companies that have already done all the risky legwork of discovering prodrugs (the compounds that show promise as future drugs), narrowing down the resulting compounds to the most promising, and maybe even getting through early clinical trials. It means the purchasing company can be fairly sure of getting something that works, and the biggest risk will be the money it invests.

Buying a company with a promising drug can cost a lot of money, as shown by Gilead's purchase of Pharmasset. The growing popularity of this approach (more than 70% of sales in successful pharmaceutical companies result from the purchase of smaller companies, rather than their own innovation)[146] means that bidding wars are common. In cases like sofosbuvir, this drives the acquisition price up far beyond the cost of

[145] Some adjustments in the length of the patent's life can be made for protracted review or regulatory delay in FDA approval.

[146] Victor Roy and Lawrence King, "Betting on Hepatitis C: How Financial Speculation in Drug Development Influences Access to Medicines," *BMJ : British Medical Journal (Online); London* 354 (July 27, 2016), http://dx.doi.org.ezproxy1.lib.asu.edu/10.1136/bmj.i3718.

development, both of the drug itself, and the other drugs the company was researching that failed for reasons of efficacy, or of safety before they made it to the market.[147]

The issue of R&D costs has been a favorite for pharmaceutical companies to trot out in response to criticism of their pricing schemes. You've probably heard it yourself. Not only does the price of a new wonder drug have to pay the costs of developing that drug, but it also has to cover all the other drugs in development at the time, including the failures. That, claim the companies, justifies high prices. The companies themselves, so goes the argument, would most assuredly go under if they weren't allowed to compensate for this.

But, as shown in the papers unearthed by the congressional investigation, even counting failed drugs, Solvaldi and its compatriots hardly breached the $500 million mark for drug development.[148] The real cost was acquiring Pharmasset. And by rolling that cost into their calculations as a development cost, Gilead did what many pharmaceutical companies do now; they count the purchase prices, inflated by bidding wars, as one more thing that a drug's eventual market price will have to repay. The money for the purchase of other companies go to investors in the company bought, not to R&D.

Once a company has made the considerable profits common in the industry, the profits need to go somewhere. Ideally, of course, they would go back to developing new drugs and, perhaps, the purchase of small companies with promising compounds. This is

[147] Victor Roy and Lawrence King, "Betting on Hepatitis C: How Financial Speculation in Drug Development Influences Access to Medicines," *BMJ : British Medical Journal (Online); London* 354 (July 27, 2016), http://dx.doi.org.ezproxy1.lib.asu.edu/10.1136/bmj.i3718.
[148] The Price of Sovaldi and its Impact on the United States Health Care System.

also a common justification. Capitalism fosters innovation. Pharmaceutical companies must charge high prices not only to pay for the development of the drug in question, not only to pay for that drug's failed compatriots, but also to pay for future drugs. The more you press the issue, the more debt each individual compound seems to shoulder for its creators.

Right?

The narrative isn't that simple. A certain amount is of course relegated to development and acquisition. For Gilead, this was about $21 billion in 2016. But not all of it. Some of it goes into stock buybacks, a common practice in the industry.[149]

What are buybacks? They're a business practice to benefit the business's shareholders, people who've bought a 'share' of the company. If you are a shareholder, you quite literally own (a very small) piece of the company. You can continue buying shares in order to increase the size of your holding in the company.

Where buybacks come in is appealing to shareholders. Shares are subject to supply and demand. If a company has a lot of shares, and a large number of them at any one time are up for sale, that means that there's more supply than demand. The value of each share declines, meaning that the current shareholders lose money if the shares are sold. If, on the other hand, there are more potential shareholders who would like to buy shares (or stock) in a company than there are available shares, the value goes up. [150]

A buyback is when a company buys a certain amount of its own stock. This lowers the number of shares available in the marketplace. The shareholders see each

[149] Roy and King, “Betting on Hepatitis C.”
[150] Roy and King.

individual share they own increase in value. If you have, for example, a thousand shares, all of which go up in value by a dollar, you can finish a day with a thousand dollars more than you started it. And if they all go down by a dollar, you can end up a thousand dollars poorer. As you can imagine, buybacks can offer a substantial financial incentive to shareholders, and also make the shares a more appealing prospect for new investors interested in acquiring shares, which in turn benefits the company.

In 2015, Gilead spent $27 billion dollars in share buybacks, funneling its profits to its shareholders.[151] This amount outstripped its purchase of Pharmasset. It dwarfed its first-year profits. It was far, far larger than the amount of cash it had on had to buy new, promising compounds and their companies, or for R&D.[152] It didn't directly contribute to the development of new drugs.

Gilead is not unique in this. Many companies do this, both in the pharmaceutical industry (Pfizer has spent something like 139 billion on buybacks before now), and outside it. Buybacks routinely dwarf R&D costs, because of the short-term profit they make for investors, and under the current model of the pharmaceutical industry, short-term profits are far more rewarding than long-term ones.[153] Gilead was making as much money as it could off of its Hepatitis C drugs before competition arrived, and before the patents expired, and it was far from unusual in doing so. The decisions Gilead had made were accepted, predictable choices within the context of business in the United States.

---

[151] Victor Roy and Lawrence King, "Betting on Hepatitis C: How Financial Speculation in Drug Development Influences Access to Medicines," *BMJ : British Medical Journal (Online); London* 354 (July 27, 2016), http://dx.doi.org.ezproxy1.lib.asu.edu/10.1136/bmj.i3718.
[152] Roy and King.
[153] Roy and King.

Unfortunately, those decisions were in stark opposition to the best interests of their customers, the millions of Hepatitis C patients waiting for a cure.

CHAPTER 8

SOFOSBUVIR VERSUS THE UNITED STATES HEALTHCARE SYSTEM(S)

Sofosbuvir arrived on the market in late 2013, and Harvoni followed it in late 2014. Both drugs did well. Within a few months, sofosbuvir (under the proprietary name Sovaldi) had run Incivek (Vertex Pharmaceuticals' Hepatitis C drug, telaprevir) off the market. Vertex discontinued production of Incivek and returned its attention to orphan diseases.[154] Gilead's second quarter sales reached $3.66 billion; by the fourth quarter, those earnings were $10.3 billion.[155] Sofosbuvir in its first year alone had almost earned back the initial cost of Pharmasset's purchase, a business move for which Gilead was castigated. Harvoni, a combination of sofosbuvir and another direct acting antiviral, ledipasvir, released in October, justified the purchase of Pharmasset still further. Harvoni, an interferon-free therapy, diverted some potential sales for sofosbuvir but netted Gilead another $2.1 billion, earning back the 11 billion purchase of Pharmasset and then some.[156]

From the patient's point of view, the release of the $1000 pill could be summed up with a single question asked by a blogger on a support website for Hepatitis C patients:

"What's the point in finding the cure when most patients are denied access?"[157]

---

[154] Carly Helfand, "Sovaldi Forces Incivek off the Hep C Market as Vertex Calls It Quits | FiercePharma," August 13, 2014, https://www.fiercepharma.com/sales-and-marketing/sovaldi-forces-incivek-off-hep-c-market-as-vertex-calls-it-quits.

[155] Andrew Pollack, "Sales of Sovaldi, New Gilead Hepatitis C Drug, Soar to $10.3 Billion," *The New York Times*, January 10, 2018, sec. Business, https://www.nytimes.com/2015/02/04/business/sales-of-sovaldi-new-gilead-hepatitis-c-drug-soar-to-10-3-billion.html; Associated Press, "Hepatitis C 'Cure' Costs $1,000, Double the Intended Price," *New York Post* (blog), July 29, 2014, https://nypost.com/2014/07/29/hepatitis-c-cure-costs-1000-double-the-intended-price/.

[156] Pollack, "Sales of Sovaldi, New Gilead Hepatitis C Drug, Soar to $10.3 Billion."

[157] Transplanted · January 5 and 2016, "The Wyden-Grassley US Senate Investigation Into The Pricing Of Sovaldi: A Report Part I," *HepatitisC.Net* (blog), January 5, 2016, https://hepatitisc.net/living/us-senate-sovaldi-part-i/.

And, more humorously from the same writer, "…never take this drug while standing over the kitchen sink."[158]

According to the World Health Organization, by 2016, 1 million people around the world had been treated for Hepatitis C using the new drugs.[159] But the total number estimated to be infected was 71 million.[160] Simply put, systems were struggling to compensate for sofosbuvir and Harvoni's cost.

In the United States, the impact of Gilead's business decisions were particularly powerful, in part due to the structure of the US healthcare system. Payers. insurance companies and government-funded healthcare programs like Medicare and Medicaid, reeled. For years, doctors had been encouraging Hepatitis C patients in the early stages of the disease to wait for the new treatments, since combination therapy was grueling and often unsuccessful. This practice, warehousing, meant that payers were not only faced with the expense of a new drug, but also with a large patient pool who had been waiting for access to these drugs. Payers panicked. In many cases, states simply couldn't afford to treat everyone who was sick with Hepatitis C, and, in order to keep costs manageable, resorted to treatment restrictions and rationing.[161]

Why was sofosbuvir's effect on the healthcare system of the United States so destabilizing? Part of the answer lies in the fact that the United States doesn't have one

---

[158] Transplanted · January 5 and 2016, "The Wyden-Grassley US Senate Investigation Into The Pricing Of Sovaldi: A Report Part I," *HepatitisC.Net* (blog), January 5, 2016, https://hepatitisc.net/living/us-senate-sovaldi-part-i/.
[159] World Health Organization, "Global Report on Access to Hepatitis c Treatment: Focus on Overcoming Barriers" (Geneva Switzerland: World Health Organization, October 2016), http://apps.who.int/iris/bitstream/10665/250625/1/WHO-HIV-2016.20-eng.pdf?ua=1.
[160] Medecins Sans Frontieres, "Hepatitis C - Not Even Close," Issue Brief, October 29, 2017, https://msfaccess.org/hepatitis-c-not-even-close.
[161] The Price of Sovaldi and its Impact on the United States Health Care System.

healthcare system. It's more accurate to say that sofosbuvir profoundly stressed the healthcare *systems* of the United States. The decision during WWII to tie healthcare to employment means that the United States doesn't have a single healthcare system, unlike most other countries.[162] What it has instead is a patchwork of different programs, each serving a different subpopulation. And this patchwork has holes—big ones.

Many people get healthcare through their jobs, through insurers or managed care organizations. Insurers simply provide coverage for healthcare in exchange for the payment of a periodic *premium,* but some insurers are also managed care organizations. Just like the name suggests, managed care organizations handle most aspects of their enrollees' healthcare. They have contracts with insurers to provide insurance. They then finance a network of providers, like hospitals and clinics, to whom for those insurers to send their patients. Managed care organizations aren't limited to private employment. Government healthcare systems like Medicare and Medicaid also use managed care organizations.[163]

Medicare is a health insurance program supported by the federal government. It covers people age 65 or older, and some younger people with disabilities, as well as individuals with end-stage renal disease. It was established in 1965 because the elderly had difficulty accessing private health insurance, then the primary form of health

[162] Leiyu Shi and Douglas A. Singh, *Essentials of the U. S. Health Care System* (Jones & Bartlett Publishers, 2009).
[163] Shi and Singh.

insurance available in the US. Medicaid was established around the same time, intended to support the very poor and disabled.[164]

The difference between the two where things like sofosbuvir are concerned is funding. Medicare is supported entirely by the federal government. Medicaid is not; individual states share funding responsibility. Each state provides a certain amount of money, and the federal government supplements it. This also means that each state determines who's eligible for Medicaid, how low the income of a Medicaid enrollee must be, and sets other conditions. The most important of those conditions in this particular case is who is eligible for which drugs under Medicaid.[165]

The Veterans Health Administration (VHA) is another publicly funded healthcare system. It handles many aspects of care, from primary care to specialists, acute to long-term, and focuses on service-related injuries and conditions. It is also the largest healthcare system in the US, with more than 1200 facilities nationwide, serving 9 million people.[166]

Unfortunately, the VHA has struggled to provide treatment where Hepatitis C is concerned. Even before the advent of DAAs, its ability to provide access to combination therapy was inconsistent. Testimony in a 2000 hearing on veterans' access to interferon described long waits, inconsistent information and access to the expensive treatment.[167]

---

[164] Shi and Singh; Center for Medicaid and CHIP Services, "What's Medicare? | Medicare," accessed September 1, 2019, https://www.medicare.gov/what-medicare-covers/your-medicare-coverage-choices/whats-medicare.
[165] Shi and Singh, *Essentials of the U. S. Health Care System*.
[166] Veterans Healthcare Administration, "About VHA - Veterans Health Administration," General Information, accessed September 2, 2019, https://www.va.gov/health/aboutvha.asp.
[167] Subcommittee on National Security Veterans Affairs and International Relations of the Committee on Government Reform, "HEPATITIS C: ACCESS, TESTING, AND TREATMENT IN THE VA HEALTH CARE SYSTEM," § Subcommittee on National Security Veterans Affairs and International Relations of

Access to direct acting antivirals followed a similar pattern. In April 2014, 4 months after Sovaldi was FDA approved and 9 months before Harvoni was approved, the Department of Veterans Affairs offered their reaction to the pricing— a panel suggested that Solvaldi only be prescribed to the sickest patients.[168]

The VHA is not alone in having difficulty managing the financial burden of Hepatitis C. While Medicare's refusal rates for Hepatitis C treatment have remained low (under 20% throughout the time treatments have been available), Medicaid's are far higher.[169]

Medicaid's origins as a healthcare system for the poor, and its split federal-state funding combine to give it distinct financial and bureaucratic problems. There is a moral stigma attached to poverty in the United States that is made particularly evident by work requirements attached to Medicaid access make it particularly evident. It also leads states to prioritize savings where Medicaid is concerned (for example, Arizona's version of Medicaid is called the Arizona Health Care Cost Containment System). In the case of Hepatitis C, the perverse incentive that this adds was on full display; in the interest of short-term savings, treating patients early in the course of illness was avoided, allowing

---

the Committee on Government Reform (2000), https://www.gpo.gov/fdsys/pkg/CHRG-106hhrg73167/pdf/CHRG-106hhrg73167.pdf.

[168] Julie Appleby, "New Hepatitis C Drugs' Price Prompts an Ethical Debate: Who Deserves to Get Them?," *Washington Post*, May 2, 2014, sec. Business, https://www.washingtonpost.com/business/new-hepatitis-c-drugs-price-prompts-an-ethical-debate-who-deserves-to-get-them/2014/05/01/73582abc-cfac-11e3-937f-d3026234b51c_story.html.

[169] Charitha Gowda et al., "Absolute Insurer Denial of Direct-Acting Antiviral Therapy for Hepatitis C: A National Specialty Pharmacy Cohort Study," *Open Forum Infectious Diseases* 5, no. 6 (June 1, 2018), https://doi.org/10.1093/ofid/ofy076; Vincent Lo Re et al., "Disparities in Absolute Denial of Modern Hepatitis C Therapy by Type of Insurance," *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association* 14, no. 7 (July 2016): 1035–43, https://doi.org/10.1016/j.cgh.2016.03.040.

the disease to progress and require more expensive interventions, such a s liver plants, later on.

Furthermore, the states have control of their respective Medicaid spending. The state shoulders some of the financial burden; the federal government the rest. This can range widely. Montana pays only 20% of its Medicaid costs, while New York pays 51.2%.[170] Federal per capita spending varies widely state by state. This is in part due to the decentralized administration of Medicaid. Different states have elected to cover different services.[171] This also means that what care you can access as a Medicaid patient is very different state by state, as is your eligibility. While the Affordable Care Act expanded Medicaid access in a number of states, other states didn't expand it at all.[172]

Medicaid's structure affected Hepatitis C direct acting antiviral access in two ways: first, the cost of sofosbuvir and Harvoni often exceeded the entire Medicaid budgets of some states, and second, access to the medications varies widely from state to state. States are not required to provide coverage for prescription drugs via Medicaid, but those that do must provide that coverage without restrictions.[173] Unfortunately, faced with the expense of sofosbuvir and Harvoni, this directive went by the wayside. States implemented many access restrictions, and the federal government's intervention was

---

[170] "Federal and State Share of Medicaid Spending," *The Henry J. Kaiser Family Foundation* (blog), October 11, 2018, https://www.kff.org/medicaid/state-indicator/federalstate-share-of-spending/.
[171] Center for Medicare and Medicaid Services, "Geographic Variation in Standardized Medicare Spending: County Level," January 2019, https://portal.cms.gov/wps/portal/unauthportal/unauthmicrostrategyreportslink?evt=2048001&src=mstrWeb.2048001&documentID=881776D811E8577F00000080EF85EDD0&visMode=0&currentViewMedia=1&Server=E48V126P&Project=OIPDA-BI_Prod&Port=0&connmode=8&ru=1&share=1&hiddensections=header,path,dockTop,dockLeft,footer.
[172] "How Medicaid Health Care Expansion Affects You," General Information, HealthCare.gov, accessed September 2, 2019, https://www.healthcare.gov/medicaid-chip/medicaid-expansion-and-you/.
[173] Center for Medicaid and CHIP Services, "Assuring Medicaid Beneficiaries Access to Hepatitis C (HCV) Drugs," November 5, 2015, https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/downloads/rx-releases/state-releases/state-rel-172.pdf.

limited to a chiding letter reminding states of their responsibilities under the Social Security Act.[174]

These access restrictions included requirements that a patient receiving one of these drugs not be using recreational drugs or alcohol, despite the evidence indicating that neither of these things had a significant effect on treatment success. To fulfill this requirement, some states require a period of time where the patient has definitely not been using drugs. This can be up to a year in states like Illinois and Mississippi, or six months in most states, including California. Other states confirm this with a urine test.[175] Patients also had to have reached a certain degree of liver damage, sometimes severe. This requires patients to wait until their liver function is already badly compromised before they can be treated.[176] Someone with Hepatitis C would have to wait until they began experiencing the painful symptoms of decompensated cirrhosis (that is, liver damage and scarring beyond what the liver can compensate) before getting treated. The patient would then would have to live with the damage that Hepatitis C had done to their liver, even if the disease were cured. To determine if someone was sick enough to merit treatment, five states required a liver biopsy, which is a painful and invasive procedure.[177]

---

[174] Center for Medicaid and CHIP Services, "Assuring Medicaid Beneficiaries Access to Hepatitis C (HCV) Drugs," November 5, 2015, https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/downloads/rx-releases/state-releases/state-rel-172.pdf.
[175] Jason Grebely et al., "Elimination of Hepatitis C Virus Infection among PWID: The Beginning of a New Era of Interferon-Free DAA Therapy," *International Journal of Drug Policy* 47 (September 1, 2017): 26–33, https://doi.org/10.1016/j.drugpo.2017.08.001; Soumitri Barua et al., "Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States," *Annals of Internal Medicine* 163, no. 3 (August 4, 2015): 215–23, https://doi.org/10.7326/M15-0406.
[176] Carolyn Y. Johnson, "Louisiana Considers Radical Step to Counter High Drug Prices: Federal Intervention," *Washington Post*, July 3, 2017, https://www.washingtonpost.com/business/economy/louisiana-considers-radical-step-to-counter-high-drug-prices-federal-intervention/2017/07/03/456b99f6-4a59-11e7-a186-60c031eab644_story.html.
[177] Mayo Clinic, "Liver Biopsy," Mayo Clinic, accessed April 2, 2019, https://www.mayoclinic.org/tests-procedures/liver-biopsy/about/pac-20394576.

While there is something to be said for guaranteeing access to treatment to the sickest first, this means people are ill, untreated, and therefore capable of spreading the disease, more capable than the population prioritized for treatment, because they may be more active since they don't feel as sick. It also means that people with early stages of the disease are being condemned to experience the awful progression of liver failure before they're treated—before they're miserable enough to qualify. And a more damaged liver means a higher likelihood they'll need further interventions, like a transplant. Liver transplants are hard enough to come by in the United States as it is, and they are expensive, difficult procedures, expensive enough to dwarf the cost of a course of treatment with Harvoni.

Other treatment restrictions required that sofosbuvir or Harvoni only be prescribed by certain types of healthcare providers, particularly specialists like hepatologists (liver specialists) or gastroenterologists (specialists in diseases of the gut). There were (and are) many other restrictions, and they vary widely among states, creating a complex patchwork system incredibly difficult to navigate.[178]

These requirements weren't actually legal under Medicaid's own laws. State Medicaid programs aren't required to provide prescription drug coverage at all, but all of

[178] Stacey B. Trooskin, Helen Reynolds, and Jay R. Kostman, "Access to Costly New Hepatitis C Drugs: Medicine, Money, and Advocacy," *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 61, no. 12 (December 15, 2015): 1825–30, https://doi.org/10.1093/cid/civ677; Soumitri Barua et al., "Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States," *Annals of Internal Medicine* 163, no. 3 (August 4, 2015): 215–23, https://doi.org/10.7326/M15-0406; Bruce Japsen, "As Pricey Hepatitis Pill Harvoni Joins Sovaldi, States Erect Medicaid Hurdles," *Forbes*, October 10, 2014, https://www.forbes.com/sites/brucejapsen/2014/10/10/as-hepatitis-pill-harvoni-joins-sovaldi-states-erect-medicaid-hurdles/; Ed Silverman, "How Illinois Allocates $84,000 Drug for Hepatitis C," *Wall Street Journal*, August 4, 2014, sec. Business, http://www.wsj.com/articles/how-illinois-allocates-84-000-drug-for-hepatitis-c-1407114940; The Price of Sovaldi and its Impact on the United States Health Care System.

them do. According to the Social Security Act, if a state Medicaid program *does* elect to provide prescription drug coverage, it's not allowed to refuse access to a drug unless it's not being used for a condition for which it's FDA approved. It can also require prior authorization, but that's it.[179] No other exceptions. Since Sovaldi and Harvoni are approved for the treatment of Hepatitis C, state Medicaid restrictions were not, and are not legal. However, the Centers for Medicare and Medicaid Services have, so far, declined to take legal action.

But state Medicaid programs didn't feel like they had a choice. There simply wasn't enough money to go around, and federal intervention was not forthcoming.

The Indian Health Service was also struggling. Responsible for 2.2 million people, the IHS is supposed to provide medical care for the population of American Indians and Alaskan Natives in the US. This group has faced systematic discrimination and disenfranchisement throughout the history of the United States, a result of the United States' often outright genocidal policies concerning them. When it comes to health, this manifests in continuing severe health disparities and a life expectancy that is 5.5 years lower than the rest of the US population. Liver diseases play a significant role in this, and American Indians and Alaskan Natives are 4.6 times as likely to die of a liver disease than the rest of the population.[180] For Hepatitis C specifically, American Indian/Alaskan

[179] Center for Medicaid and CHIP Services, "Assuring Medicaid Beneficiaries Access to Hepatitis C (HCV) Drugs," November 5, 2015.
[180] Indian Health Service, "Disparities | Fact Sheets," *Indian Health Service Newsroom*, January 1, 2013, https://www.ihs.gov/newsroom/factsheets/disparities/.

Natives die at more than twice the rate of the rest of the US population (12.2 per 100,000 as versus 5.0 per 100,000). [181]

IHS was constrained by a small budget. Its expenditures per person were only about $3099 per year, not nearly enough to cover a course of sofosbuvir or Harvoni. Most American Indian/Alaskan Native households earn less than $30,000 per year, putting out-of-pocket costs for sofosbuvir or Harvoni well out of reach. As late as 2016, IHS had not received any supplemental funding to support Hepatitis C treatment in the communities it served. It, too, instituted access barriers.[182] These access barriers may be loosening. IHS just got $25 million to combat Hepatitis C … but this $25 million is bundled with an HIV program, so it's unknown how much will actually go to combatting Hepatitis C.[183]

The prison system was also heavily affected, with very few prisoners getting access to treatment. Here too, it was a story of the cost of Hepatitis C medication exceeding the entire healthcare budget for parts of the system. Gilead had opted not to negotiate contracts for lower prices with 45 state prison systems, because smaller state prison systems didn't offer significant profits.[184] As a result, few prisoners could access treatment, despite representing nearly a third of all Hepatitis C patients in the United States.[185] Prisons also expose their inmates to much higher risk of bloodborne infections.

---

[181] Jessica Leston and Joe Finkbonner, "The Need to Expand Access to Hepatitis C Virus Drugs in the Indian Health Service," *JAMA* 316, no. 8 (August 23, 2016): 817, https://doi.org/10.1001/jama.2016.7186.
[182] Leston and Finkbonner.
[183] Indian Health Service, "Indian Health Service Highlights Initiative to Eliminate Hepatitis C and HIV/AIDS in Indian Country during National Native HIV/AIDS Awareness Day | 2019 Press Releases," *Indian Health Service Newsroom*, March 19, 2019, https://www.ihs.gov/newsroom/pressreleases/2019pressreleases/indian-health-service-highlights-initiative-to-eliminate-hepatitis-c-and-hiv-aids-in-indian-country-during-national-native-hiv-aids-awareness-day/.
[184] The Price of Sovaldi and its Impact on the United States Health Care System.
[185] Beckman et al., "New Hepatitis C Drugs Are Very Costly And Unavailable To Many State Prisoners," October 2016.

Inequitable access to medical care in prisons is a persistent problem.[186] In short, prisoners are both more likely to have Hepatitis C or get it once they're incarcerated, making them a vital population to treat from a public health point of view. But the money simply wasn't there. The prices Gilead charged state prison systems were so high that in some cases the cost of treating all Hepatitis C patients in some state prison systems exceeded the entire state prison medical budget.[187] Since new guidelines require states to treat prisoners with direct acting antivirals, and these direct acting antivirals are prohibitively expensive, this means that many prisoners aren't getting treated for Hepatitis C at all.[188] By 2016, (three years after Sovaldi's approval) only 0.89% of all prisoners diagnosed with Hepatitis C in the United States were receiving treatment. Spending by the Bureau of Prisons on Hepatitis C drugs increased by 14%, even though the number of people actually getting the treatments decreased by more than half.[189]

The socioeconomic impacts of imprisonment bar released individuals from access to treatment. These are the same factors that can increase the likelihood of a relapse into

---

[186] Burton, Reilly, and Penman, "Incarceration as a Risk Factor for Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-Infection in Mississippi"; Andy Marso, "Locked out of Care: Brain Fungus Death Points to Extensive Problems in Kansas Prisons," *Kansas City Star*, April 28, 2019, https://www.kansascity.com/news/business/health-care/article229423849.html; Steve Coll, "The Jail Health-Care Crisis," New Yorker, February 25, 2019, https://www.newyorker.com/magazine/2019/03/04/the-jail-health-care-crisis; FIELDS v. CORIZON HEALTH, | Case No. 2:09-cv-529... | 20120120987| Leagle.com (United States District Court, M.D. Florida, Fort Myers Division January 19, 2012).

[187] Alex Smith, "Missouri Faces Costly Dilemma: How To Treat Inmates With Hepatitis C?," *NPR.Org*, January 19, 2018, https://www.npr.org/sections/health-shots/2018/01/19/578425032/missouri-faces-costly-dilemma-how-to-treat-inmates-with-hepatitis-c; Adam L. Beckman et al., "New Hepatitis C Drugs Are Very Costly And Unavailable To Many State Prisoners," *Health Affairs; Chevy Chase* 35, no. 10 (October 2016): 1893–1901, http://dx.doi.org.ezproxy1.lib.asu.edu/10.1377/hlthaff.2016.0296.

[188] Alex Smith, "Missouri Faces Costly Dilemma: How To Treat Inmates With Hepatitis C?," *NPR.Org*, January 19, 2018, https://www.npr.org/sections/health-shots/2018/01/19/578425032/missouri-faces-costly-dilemma-how-to-treat-inmates-with-hepatitis-c

[189] The Price of Sovaldi and its Impact on the United States Health Care System, § COMMITTEE ON FINANCE UNITED STATES SENATE (2015)

drug use, making it still more likely that the individual in question can transmit the disease further. The existing system withholds treatment from those who need it most, and are the most likely to transmit the infection. This is the opposite of an effective public health strategy.

Harm reduction groups, like the one I spoke to in the process of researching this dissertation, recognize this. As a result, healthcare providers trying to increase treatment for Hepatitis C patients who inject drugs have a wide variety of strategies they use to obtain treatment for their patients. They help in navigating the labyrinthine bureaucracy of state Medicaid systems. They help patients apply for grants to fund their treatment. In some places, they substitute their own urine for that of their patients, so treatment won't be withheld because of a failed drug test. And in some places, they practice what is called 'reimportation' of drugs; purchasing the necessary medications abroad, where they are affordable, and bringing them back to the patients who need them.[190]

Because the criminalization of injection drug use leads to incarceration, better access to treatment in prison would have a dramatic effect on preventing Hepatitis C. But only a handful of state prison systems were given access to DAAs at a lower price. Prison access to direct acting antivirals remains low, and as a result, transmission remains high. Likewise, the sobriety requirements implemented by Medicaid programs block other high-risk groups from accessing the medications they need. In their attempts to cut costs, **public payers had blocked the most afflicted groups from access to treatment, leaving Hepatitis C essentially uncontrolled in the communities where its spread was highest.**

[190] Anonymous Provider or Patient Interview, n.d.

These access barriers did not go unremarked. On July 11th, 2014, Gilead got the congressional attention it had hoped to avoid by lowering its pricing from the proposed $121,000 to $84,000. Senators Ron Wyden of Oregon and Charles Grassley of Iowa sent a letter requesting information about the pricing of Sovaldi to the CEO of Gilead, Dr. John C. Martin. This was the first step in opening a Committee on Finance investigation into Gilead's pricing.

What does it take to trigger a Senate investigation? Generally, they must be instigated by a committee, and be relevant to an aspect of public policy. Investigations are authorized through resolutions, setting out the scope and goals of the investigation, which is then carried out by the committee. The end result is information that lawmakers can use when making policy.[191]

In this case, Senators Wyden and Grassley drew their justification for the investigation from the effects of Hep C drug pricing on public payer systems such as Medicaid. Because the federal government funded these systems, the federal government was due an explanation from Gilead for the pricing of Sovaldi and Harvoni.

To achieve this, Wyden and Grassley requested a wide range of documents from Gilead. They wanted documentation including the whole process of acquiring and pricing the drugs, of R&D costs, of Gilead's communications with its financial advisors, of the potential effects of Harvoni (then in the FDA approval process) on Sovaldi's price, and of

[191] "U.S. Senate: A History of Notable Senate Investigations," United States Senate, accessed March 27, 2019, https://www.senate.gov/artandhistory/history/common/briefing/Investigations.htm#2.

Gilead's interactions with the American Association for the Study of the Liver and the Infectious Diseases Society of America.[192]

This last request was because the American Association for the Study of the Liver, and the Infectious Diseases Society of America both played a role in setting treatment guidelines. But of the 27 members of the panel making the recommendations, 18 had some kind of financial tie to Gilead. The Committee on Finance wanted to understand the exact nature of these relationships, as the American Association for the Study of the Liver recommendations maintained Sovaldi as a backbone of treatment for Hep C. [193]

Gilead had 60 days to provide the requested documents, which it did… mostly. Missing were documents regarding the amount it had cost for Gilead to finish research and development of Sovaldi. The resulting bulk of documentation—20,000 pages of documents from Gilead alone—took Senate staffers 18 months to review. The result was a 134 page report, that detailed the sequence of events leading up to Gilead's purchase of Pharmasset, and its subsequent pricing decisions.[194]

The Senate report concluded that the primary factor in pricing sofosbuvir and Harvoni had been maximizing profit while keeping public scrutiny low. Lower price points had been considered and rejected, even though they would have allowed Gilead to

[192] "Senators Seek Details on Sovaldi Pricing | Chuck Grassley," Chuck Grassley: Unted States Senator For Iowa, July 11, 2014, https://www.grassley.senate.gov/news/news-releases/senators-seek-details-sovaldi-pricing.
[193] "Senators Seek Details on Sovaldi Pricing | Chuck Grassley"; "Hepatitis C Guidance: AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected with Hepatitis C Virus," *Hepatology* 62, no. 3 (September 1, 2015): 932–54, https://doi.org/10.1002/hep.27950.
[194] "Wyden-Grassley Sovaldi Investigation Finds Revenue-Driven Pricing Strategy Behind $84,000 Hepatitis Drug | U.S. Senator Ron Wyden of Oregon," Ron Wyden: United States Senator for Oregon, December 1, 2015, https://www.wyden.senate.gov/news/press-releases/wyden-grassley-sovaldi-investigation-finds-revenue-driven-pricing-strategy-behind-84000-hepatitis-drug.

recoup their developmental costs, despite Gilead's own pricing advisors voicing their concerns that the higher price points would significantly impede access. Gilead had also placed the needs of entities like Medicaid and most state prison systems as low to middling priority, and declined to offer rebates large enough to enable these systems to obtain the drug.

Gilead had considered higher price points as well, and had anticipated the probable backlash and potential congressional investigation. They'd been off in their calculations. But the sole outcome of the congressional inquiry was an appropriation for funding for the treatment of veterans with Hepatitis C through the VA: a budget of 1 billion to assist VA access to Hepatitis C DAAs.[195] The VA has since struck a deal with Gilead to lower DAA prices to a more affordable level, of around $12,500 per course of treatment.[196]

The rest of the market was left to correct itself.

In pricing sofosbuvir at $84,000 per course of treatment, Gilead had made a choice to prioritize getting more money from each sale over making more sales. Had Gilead chosen to price the drug at a lower level, it is entirely possible it would have seen the same revenue from sofosbuvir because more patients would have started treatment. The subsequent volume of patients would have made up for the lower price.

Gilead continued to profit. By that point in December 2015, Gilead had made more than 20 billion dollars from sales *in the United States alone*. 8 billion of that had

[195] Leston and Finkbonner, "The Need to Expand Access to Hepatitis C Virus Drugs in the Indian Health Service."
[196] Ed Silverman, "The VA Got a Good Price for a Hep C Drug. Why Not Medicare?," *STAT*, March 7, 2017, https://www.statnews.com/pharmalot/2017/03/07/veternas-hepatitis-c-drug-prices/.

been from Medicare and Medicaid, even with treatment being rationed. The purchase of Pharmasset could almost have been paid for twice over by Gilead's profits in those first 18 months.

The congressional inquiry had some impact on publicly funded programs like the VA, but they weren't the only ones feeling pinched. Even private health plans were refusing treatment and instituting difficult-to-meet requirements. Shortly after the launch of Sovaldi, and before the launch of Harvoni, the California Technology Assessment Forum, sponsored by the insurance group Blue Cross/Blue Shield, issued an official recommendation that patients in early stages of the disease should wait for treatment, just like Medicare and Medicaid. Further warehousing of patients was proposed, as sofosbuvir needed to be combined with interferon.[197] Harvoni (a combination of sofosbuvir and ledipasvir, another direct acting antiviral), was likely to be approved and released that fall as an interferon-free treatment. It wouldn't need to be taken with interferon. Patients should wait for a better drug, never mind that Harvoni was likely to be even more expensive.

Despite these recommendations, access to the drugs on private insurance plans was higher, at least at first. A 2015 study found that 10.2% of prescriptions for private insurance reimbursement were refused, versus 46.3% for Medicaid. Medicare did better, with only 5% of requests refused. These refusals were what are called absolute denials; an initial denial of the prescription can be appealed, but if the appeal is refused, the patient has no further recourse.[198] But when the authors did a follow-up survey in 2018,

[197] Appleby, "New Hepatitis C Drugs' Price Prompts an Ethical Debate."
[198] Re et al., "Disparities in Absolute Denial of Modern Hepatitis C Therapy by Type of Insurance."

they found that private insurance had a refusal rate of 52.4%. Think about that for a minute—if you're on commercial insurance, such as the insurance you might get through work, and you have Hepatitis C and get a prescription from your doctor for something that has over a 90% chance of curing you, you're more likely to be refused treatment by your insurance than not.[199] This study was done (unlike the previous one) with a national pharmacy service, and included 9025 patients. 3200 of those patients, over a third, were refused treatment. And even worse, as the study progressed, the rate of refusal went *up.* Only Medicaid had shown an improvement: 34.5% refusal rate was down from its 2015 46.3%. Medicare's refusal rates had risen to 14.7% from 10%. In short, despite market competition, the situation worsened between 2015 and 2018.[200]

So what are the criteria insurers are enforcing?

Out of curiosity, I looked up the requirements for access to Hepatitis C treatment of my own insurer, Aetna. Were I to be diagnosed with Hepatitis C tomorrow, I would need to undergo a liver biopsy, which is an incredibly uncomfortable procedure. A needle is inserted into your side and into the liver. There are other ways of doing a liver biopsy, but they are also unpleasant. A transjugular one, for example, uses the jugular vein in the neck.[201]

After enduring this procedure, you also have to demonstrate that your fibrosis, or scarring of your liver, has been evaluated in a series of tests and scores. You have to undergo medical imaging to show there's actual damage to your liver that's having effects

[199] Gowda et al., "Absolute Insurer Denial of Direct-Acting Antiviral Therapy for Hepatitis C."
[200] Gowda et al.
[201] Aetna, "Hepatitis C - Pharmacy Clinical Policy Bulletins Aetna Non-Medicare Prescription Drug Plan," Aetna, August 6, 2015, http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html.

on the rest of your body. Whether or not you do all these things, you then get to navigate a maze of diagnoses and previous treatment experience to determine which direct acting antiviral, if any, your insurer will cover for you.

Aetna covers, theoretically, a whole bunch of direct acting antivirals. But the ones that don't require combination therapy all have long lists of requirements, including liver biopsies.[202] Suffice it to say that I, like many other Americans, sincerely hope not to get Hepatitis C while dependent on my current insurance.

What about Medicaid requirements? I live in Arizona, where the state branch of Medicaid is the Arizona Health Care Cost Containment System (AHCCCS). Unlike some other states, it doesn't require that the patient have reached a particular stage of liver damage in order to be eligible for treatment. It does, however, require three months since the last time the patient used recreational drugs, and that, if applicable, the patient be enrolled in a substance abuse program. It also requires that treatment be monitored. And if you were previously treated but not adherent to that treatment, you're out of luck. You're forbidden from accessing once more the drugs you need to treat Hepatitis C.[203]

Nationwide, both liver damage restrictions and sobriety requirements are common. Arizona has a lot of Hepatitis C patients (about 90,000 people, as of 2017).[204] But it is not alone in the barriers it erects to treatment. Around the United States, Hepatitis C patients navigate systems replete with unscientific (one justification for

---

[202] Aetna.
[203] Arizona Health Care Cost Containment System, "AHCCCS Medical Policy Manual: Section 320 - Services With Special Circumstances: Hepatitis C Virus (HCV) Prior Authorization Requirements for Direct Acting Antiviral Treatment" (State of Arizona, 7/112018), https://www.azahcccs.gov/shared/Downloads/MedicalPolicyManual/300/320-N.pdf.
[204] "Hepatitis C: State of Medicaid Access Report Card" (Center for Health Law and Policy Innovation Harvard Law School, 2017).

sobriety requirements is a concern about reinfection rates, which studies have showed to be fairly low, and easily reduced through safety training)[205] and perverse (treating only the sickest patients allows the disease to spread further) requirements. And private insurance, like mine, has set up equally difficult barriers. For patients on AHCCCS, they must navigate a system that seeks to determine whether they're compliant with treatment, and that they're not using drugs. For patients with private insurance like Aetna, they must prove they're sick enough, and that they're in the right group that's likely to respond to treatment—giving their insurers the biggest bang for their buck, as it were.

The reaction of both public and private payers to high drug prices was uniformly to clamp down on access, prioritizing cost containment over health. Ironically, this reaction meant patients became sicker, requiring more expensive interventions as their disease progressed. When this fractured healthcare system ran up against Gilead's revenue-maximizing behavior (perfectly acceptable, and indeed encouraged, in the business realm), the result created conditions that allow Hepatitis C infection to spread in the face of a cure.

[205] Jason Grebely et al., "Elimination of Hepatitis C Virus Infection among PWID: The Beginning of a New Era of Interferon-Free DAA Therapy," *International Journal of Drug Policy* 47 (September 1, 2017): 26–33, https://doi.org/10.1016/j.drugpo.2017.08.001; T. Jake Liang and John W. Ward, "Hepatitis C in Injection-Drug Users — A Hidden Danger of the Opioid Epidemic," *New England Journal of Medicine* 378, no. 13 (March 29, 2018): 1169–71, https://doi.org/10.1056/NEJMp1716871.

CHAPTER 9

"THE NETFLIX MODEL" OR HOW LOUISIANA STOPPED WORRYING AND LOVED THE PRICE TAG

2017 found Louisiana, like many states in the US, with a serious Hepatitis C problem. In fact, it had more of a Hepatitis C problem than most other states and it's one of the poorest states in the country. Direct acting antivirals should have been a literal lifesaver, and sofosbuvir had been approved almost four years earlier. But the lifesaving treatments weren't getting to patients, because the state didn't have the money to provide them for Medicaid or its prison system.[206]

In 2016, these restrictions meant that only 324 of the state's 35,000 Hepatitis C patients who were on Medicaid or uninsured received treatment. The rest had to wait until Hepatitis C destroyed their livers enough to make them eligible for treatment, a situation full of cruel ironies like doctors telling patients they were "lucky" for having livers damaged enough that they met criteria for treatment.[207]

The state was in an impossible position. It didn't have the $764 million that it would take to treat all its patients, and Gilead's cost reduction programs would only apply if the state promised to treat all its patients at a lowered sum, which would still have been well beyond the Medicaid budget. The state responded by rationing treatment however it could. It instituted liver damage requirements. It also instituted sobriety requirements.

[206] Rebekah Gee, "Louisiana's Journey Toward Eliminating Hepatitis C | Health Affairs," *Health Affairs Blog* (blog), April 1, 2019, https://www.healthaffairs.org/do/10.1377/hblog20190327.603623/full/.
[207] Johnson, "Louisiana Considers Radical Step to Counter High Drug Prices," July 3, 2017.

Neither of these were good practices from a clinical or public health standpoint, or from the point of view of patients or clinicians.[208]

Faced with the quandary, Louisiana's Secretary of Health, Rebekah Gee, tried a new approach. Negotiations for lower prices had failed, so the Louisiana Department of Health began looking into a law from 1910, called Section 1498, a part of federal intellectual property law.[209] §1498 allows the federal government to 'take over' a patent, letting another company produce the product for government use while compensating the patent holder at what the government deems a fair price. Though it's fallen out of favor recently, §1498 has been used heavily in the past, and has a robust body of precedence to support its use to obtain a wide variety of products.[210]

§1498 has allowed the government access to patented materials at affordable prices. The traditional compensation has been 10% of royalties from the manufactured good. The law itself, and its use, is a cousin of *eminent domain*, the process by which the federal government can buy private land for a price that it, not the seller, sets. Eminent domain saw heavy use when the United States was building railways, since it stopped landowners who owned land adjacent to railways from raising their land prices to unaffordable levels.[211] It's also the process by which some land is being appropriated for the border wall proposed by President Trump. It's a controversial, but well-established law with many precedents for its use.

---

[208] Johnson.
[209] Gee, "Louisiana's Journey Toward Eliminating Hepatitis C | Health Affairs."
[210] "U.S.C. Title 28 Sec. 1498," 28 U.S.C § 1498 (1910), https://www.govinfo.gov/content/pkg/USCODE-2011-title28/html/USCODE-2011-title28-partIV-chap91-sec1498.htm.
[211] Amy Kapczynski and Aaron S. Kesselheim, "'Government Patent Use': A Legal Approach To Reducing Drug Spending," *Health Affairs* 35, no. 5 (May 1, 2016): 791–97, https://doi.org/10.1377/hlthaff.2015.1120.

§1498 was originally passed in 1910 to guarantee patentholders whose patents had been infringed upon by the government recompense. Prior to its passage, the federal government had immunity for patent infringement; §1498 guarenteed patentholders some repayment, but did not allow them to petition a court to order the government to stop infringing their patents. It also explicitly codified the federal government's ability to infringe patents, including for defense or for use for the benefit of the public. In the early 1940s, in part driven by concerns about wartime price gouging, Congress expanded §1498's powers still further, allowing subcontractors working for the government to be covered as well. The letter of the law has not changed since then.[212]

A ruling in 1958 expanded the use of §1498 still further, encouraging its use to obtain medications throughout the 1950s and 1960s. This included the use of §1498 to purchase an antibiotic from an Italian supplier even though the patentholder was already in negotiations with the federal government. The reason for this was that the Italian manufacturer's price was 78% lower than that the patentholder was offering. By the 1950s, government employees considering the purchase of patented materials were encouraged to keep the usage of §1498 as an option. Upset, a pharmaceutical industry group tried to curtail the powers of §1498, but were unsuccessful.[213]

§1498 was, and is, a powerful tool. Were we to use it in accordance with the precedence set by its use in the 1950s and 1960s, it would be entirely possible to justify the compulsory licensing of sofosbuvir on the basis of its price alone. But §1498's use in

[212] Hannah Brennan et al., "A Prescription for Excessive Drug Pricing: Leveraging Government Patent Use for Health," *Yale Journal of Law and Technology* 18, no. 1 (April 2, 2017), https://digitalcommons.law.yale.edu/yjolt/vol18/iss1/7.
[213] Brennan et al.

the pharmaceutical realm has fallen out of fashion, even though many federal agencies use it for other patented materials. In the 1970s, the federal government stopped using §1498 for pharmaceutical products.[214] The closest the federal government has come to using §1498 for medications since then was a result of the 2001 anthrax scare.

Cipro (ciprofloxin), is an antibiotic that can be used to treat anthrax. If taken after exposure, Cipro prevents the patient from getting the disease. But the manufacturer of Cipro, Bayer, wouldn't lower the price. Federal health officials discussed invoking 1498, and Bayer retreated, making the drug available at a price that the federal government could afford.[215] In that case, §1498 never needed to be invoked.

Pharmaceutical companies are understandably reluctant to let the use of §1498 become a norm once again. It would usher in a new era in healthcare, where unavailability of a drug could trigger federal compulsory licensing of a patent.

The revivification of the use of §1498 is a threatening prospect to pharmaceutical companies, but the political reluctance to use the law again makes it an unlikely solution to the situation. Louisiana's plea that §1498 be invoked was a case in point. During the open comment period on the move, the Department of Commerce submitted a comment directly opposing the use of §1498. Its arguments were that Gilead would certainly take legal action against the administration, resulting in a costly and lengthy court battle that might, in cost, exceed the expense of simply paying for the medication at Gilead's market

[214] Brennan et al.
[215] Keith Bradsher With Edmund L. Andrews, "A NATION CHALLENGED: CIPRO; U.S. Says Bayer Will Cut Cost of Its Anthrax Drug," *The New York Times*, October 24, 2001, sec. Business, https://www.nytimes.com/2001/10/24/business/a-nation-challenged-cipro-us-says-bayer-will-cut-cost-of-its-anthrax-drug.html.

rate, and that to invoke §1498 in that case would set a dangerous precedent that would discourage innovation in the pharmaceutical industry.[216]

Without federal support, the use of §1498 was impossible, as it's a federal law that states cannot invoke. The federal government has to be the one to enforce it. Louisiana had to find a different solution.

That solution came in the form of the 'Netflix model'. Louisiana is the first state to reach a deal of this nature with Gilead (more correctly, Gilead's subsidiary, Asegua Theraputics, which sells the generic versions of Harvoni), with potential far-reaching consequences for other states. Louisiana has agreed to pay Gilead a set sum a year for access to as much of the medications as it can use. The advantage of this will be clearest in the early years as the state can treat a lot of people very quickly. Later years of the deal, the state may be paying more than it would have cost to simply purchase the treatment outright. But it's opened a path to rapid elimination.[217] The state of Washington followed suit.[218]

Still, §1498 remains on the books, and it has been used to obtain lower-priced medications in the past. There are other, similar laws, such as the Bayh-Dole Act and its requirement that federally-funded inventions allow the public to access the invention, or the federal government may intervene. Once §1498 is used again, and if the courts uphold

---

[216] "Secretary Alex Azar's Comment on 28 USC 1498 Submitted for the Record of the 2018 Confirmation Hearings," *Knowledge Ecology International* (blog), August 1, 2018, https://www.keionline.org/28631.
[217] Selena Simmons-Duffin, "Louisiana's Novel 'Subscription' Model For Pricey Hepatitis C Drugs Gains Approval," *NPR*, June 26, 2019, https://www.npr.org/sections/health-shots/2019/06/26/736312262/louisianas-novel-subscription-model-for-pricey-hepatitis-c-drugs-gains-approval.
[218] JoNel Aleccia, Barbara Feder Ostrov, and Donna Gordon Blankinship, "As AbbVie Fights Hepatitis C, States Make Secret Deals with Drugmakers," *USA Today*, accessed October 25, 2019, https://www.usatoday.com/story/news/health/2019/10/25/abbvie-fights-hepatitis-c-states-make-secret-deals-drugmakers/4087441002/.

its use, which seems likely giving existing precedent, it might offer a partial solution to drug pricing in the United States, allowing the federal government to limit drug prices by intervening when a drug's pricing undermines its public health potential.

We've balanced public health with pharmaceutical profit successfully before. One example of this is the story of penicillin—or more appropriately, the story of how we learned to produce penicillin in large quantities. Penicillin was extremely difficult and expensive to produce, but collaborations between government laboratories and the pharmaceutical industry not only solved the problem of its production, but produced a cheap and easily available drug which we use to this day.

CHAPTER 10

THE STORY OF PENICILLIN

2017 found Louisiana, like many states in the US, with a serious Hepatitis C problem. In fact, it had more of a Hepatitis C problem than most other states and it's one of the poorest states in the country. Direct acting antivirals should have been a literal lifesaver, and sofosbuvir had been approved almost four years earlier. But the lifesaving treatments weren't getting to patients, because the state didn't have the money to provide them for Medicaid or its prison system.[219]

In 2016, these restrictions meant that only 324 of the state's 35,000 Hepatitis C patients who were on Medicaid or uninsured received treatment. The rest had to wait until Hepatitis C destroyed their livers enough to make them eligible for treatment, a situation full of cruel ironies like doctors telling patients they were "lucky" for having livers damaged enough that they met criteria for treatment.[220]

The state was in an impossible position. It didn't have the $764 million that it would take to treat all its patients, and Gilead's cost reduction programs would only apply if the state promised to treat all its patients at a lowered sum, which would still have been well beyond the Medicaid budget. The state responded by rationing treatment however it could. It instituted liver damage requirements. It also instituted sobriety requirements. Neither of these were good practices from a clinical or public health standpoint, or from the point of view of patients or clinicians.[221]

---

[219] Rebekah Gee, "Louisiana's Journey Toward Eliminating Hepatitis C | Health Affairs," *Health Affairs Blog* (blog), April 1, 2019, https://www.healthaffairs.org/do/10.1377/hblog20190327.603623/full/.
[220] Johnson, "Louisiana Considers Radical Step to Counter High Drug Prices," July 3, 2017.
[221] Johnson.

Faced with the quandary, Louisiana's Secretary of Health, Rebekah Gee, tried a new approach. Negotiations for lower prices had failed, so the Louisiana Department of Health began looking into a law from 1910, called Section 1498, a part of federal intellectual property law.[222] §1498 allows the federal government to 'take over' a patent, letting another company produce the product for government use while compensating the patent holder at what the government deems a fair price. Though it's fallen out of favor recently, §1498 has been used heavily in the past, and has a robust body of precedence to support its use to obtain a wide variety of products.[223]

§1498 has allowed the government access to patented materials at affordable prices. The traditional compensation has been 10% of royalties from the manufactured good. The law itself, and its use, is a cousin of *eminent domain*, the process by which the federal government can buy private land for a price that it, not the seller, sets. Eminent domain saw heavy use when the United States was building railways, since it stopped landowners who owned land adjacent to railways from raising their land prices to unaffordable levels.[224] It's also the process by which some land is being appropriated for the border wall proposed by President Trump. It's a controversial, but well-established law with many precedents for its use.

§1498 was originally passed in 1910 to guarantee patentholders whose patents had been infringed upon by the government recompense. Prior to its passage, the federal

---

[222] Gee, "Louisiana's Journey Toward Eliminating Hepatitis C | Health Affairs."
[223] "U.S.C. Title 28 Sec. 1498," 28 U.S.C § 1498 (1910), https://www.govinfo.gov/content/pkg/USCODE-2011-title28/html/USCODE-2011-title28-partIV-chap91-sec1498.htm.
[224] Amy Kapczynski and Aaron S. Kesselheim, "'Government Patent Use': A Legal Approach To Reducing Drug Spending," *Health Affairs* 35, no. 5 (May 1, 2016): 791–97, https://doi.org/10.1377/hlthaff.2015.1120.

government had immunity for patent infringement; §1498 guarenteed patentholders some repayment, but did not allow them to petition a court to order the government to stop infringing their patents. It also explicitly codified the federal government's ability to infringe patents, including for defense or for use for the benefit of the public. In the early 1940s, in part driven by concerns about wartime price gouging, Congress expanded §1498's powers still further, allowing subcontractors working for the government to be covered as well. The letter of the law has not changed since then.[225]

A ruling in 1958 expanded the use of §1498 still further, encouraging its use to obtain medications throughout the 1950s and 1960s. This included the use of §1498 to purchase an antibiotic from an Italian supplier even though the patentholder was already in negotiations with the federal government. The reason for this was that the Italian manufacturer's price was 78% lower than that the patentholder was offering. By the 1950s, government employees considering the purchase of patented materials were encouraged to keep the usage of §1498 as an option. Upset, a pharmaceutical industry group tried to curtail the powers of §1498, but were unsuccessful.[226]

§1498 was, and is, a powerful tool. Were we to use it in accordance with the precedence set by its use in the 1950s and 1960s, it would be entirely possible to justify the compulsory licensing of sofosbuvir on the basis of its price alone. But §1498's use in the pharmaceutical realm has fallen out of fashion, even though many federal agencies use it for other patented materials. In the 1970s, the federal government stopped using

[225] Hannah Brennan et al., "A Prescription for Excessive Drug Pricing: Leveraging Government Patent Use for Health," *Yale Journal of Law and Technology* 18, no. 1 (April 2, 2017), https://digitalcommons.law.yale.edu/yjolt/vol18/iss1/7.
[226] Brennan et al.

§1498 for pharmaceutical products.[227] The closest the federal government has come to using §1498 for medications since then was a result of the 2001 anthrax scare.

Cipro (ciprofloxin), is an antibiotic that can be used to treat anthrax. If taken after exposure, Cipro prevents the patient from getting the disease. But the manufacturer of Cipro, Bayer, wouldn't lower the price. Federal health officials discussed invoking 1498, and Bayer retreated, making the drug available at a price that the federal government could afford.[228] In that case, §1498 never needed to be invoked.

Pharmaceutical companies are understandably reluctant to let the use of §1498 become a norm once again. It would usher in a new era in healthcare, where unavailability of a drug could trigger federal compulsory licensing of a patent.

The revivification of the use of §1498 is a threatening prospect to pharmaceutical companies, but the political reluctance to use the law again makes it an unlikely solution to the situation. Louisiana's plea that §1498 be invoked was a case in point. During the open comment period on the move, the Department of Commerce submitted a comment directly opposing the use of §1498. Its arguments were that Gilead would certainly take legal action against the administration, resulting in a costly and lengthy court battle that might, in cost, exceed the expense of simply paying for the medication at Gilead's market rate, and that to invoke §1498 in that case would set a dangerous precedent that would discourage innovation in the pharmaceutical industry.[229]

---

[227] Brennan et al.
[228] Keith Bradsher With Edmund L. Andrews, "A NATION CHALLENGED: CIPRO; U.S. Says Bayer Will Cut Cost of Its Anthrax Drug," *The New York Times*, October 24, 2001, sec. Business, https://www.nytimes.com/2001/10/24/business/a-nation-challenged-cipro-us-says-bayer-will-cut-cost-of-its-anthrax-drug.html.
[229] "Secretary Alex Azar's Comment on 28 USC 1498 Submitted for the Record of the 2018 Confirmation Hearings," *Knowledge Ecology International* (blog), August 1, 2018, https://www.keionline.org/28631.

Without federal support, the use of §1498 was impossible, as it's a federal law that states cannot invoke. The federal government has to be the one to enforce it. Louisiana had to find a different solution.

That solution came in the form of the 'Netflix model'. Louisiana is the first state to reach a deal of this nature with Gilead (more correctly, Gilead's subsidiary, Asegua Theraputics, which sells the generic versions of Harvoni), with potential far-reaching consequences for other states. Louisiana has agreed to pay Gilead a set sum a year for access to as much of the medications as it can use. The advantage of this will be clearest in the early years as the state can treat a lot of people very quickly. Later years of the deal, the state may be paying more than it would have cost to simply purchase the treatment outright. But it's opened a path to rapid elimination.[230] The state of Washington followed suit.[231]

Still, §1498 remains on the books, and it has been used to obtain lower-priced medications in the past. There are other, similar laws, such as the Bayh-Dole Act and its requirement that federally-funded inventions allow the public to access the invention, or the federal government may intervene. Once §1498 is used again, and if the courts uphold its use, which seems likely giving existing precedent, it might offer a partial solution to drug pricing in the United States, allowing the federal government to limit drug prices by intervening when a drug's pricing undermines its public health potential.

---

[230] Selena Simmons-Duffin, "Louisiana's Novel 'Subscription' Model For Pricey Hepatitis C Drugs Gains Approval," *NPR*, June 26, 2019, https://www.npr.org/sections/health-shots/2019/06/26/736312262/louisianas-novel-subscription-model-for-pricey-hepatitis-c-drugs-gains-approval.

[231] JoNel Aleccia, Barbara Feder Ostrov, and Donna Gordon Blankinship, "As AbbVie Fights Hepatitis C, States Make Secret Deals with Drugmakers," *USA Today*, accessed October 25, 2019, https://www.usatoday.com/story/news/health/2019/10/25/abbvie-fights-hepatitis-c-states-make-secret-deals-drugmakers/4087441002/.

We've balanced public health with pharmaceutical profit successfully before. One example of this is the story of penicillin—or more appropriately, the story of how we learned to produce penicillin in large quantities. Penicillin was extremely difficult and expensive to produce, but collaborations between government laboratories and the pharmaceutical industry not only solved the problem of its production, but produced a cheap and easily available drug which we use to this day.

CHAPTER 11

THE 12.5 BILLION DOLLAR QUESTION

The story that sofosbuvir's creators told, and that this book has recounted, was a straightforward one, and a traditional one. A terrible disease existed, one without an effective cure, dooming millions to suffer its ravages. A group of dedicated scientists in a plucky startup company discovered a potentially miraculous compound. Against the odds, with cleverness and grit, they refined it to reach its full potential as a cure for an intractable illness. Certainly, it was priced high, but didn't this reflect the worth of the drug?

There are, however, complications in the story of sofosbuvir. They range from Merck's lawsuit against Gilead, claiming that sofosbuvir infringes on one of Merck's patents, the lawsuits of one of the drug's early inventors against Pharmasset, and the question of whether sofosbuvir received federal funding and is therefore subject to the Bayh-Dole Act of 1980.

In 2016, Gilead lost a patent lawsuit for sofosbuvir to Merck, another large pharmaceutical company, and was ordered to pay $200 million. Merck claimed that it had patented sofosbuvir before Gilead had, and therefore Gilead's marketing of sofosbuvir was patent infringement. It claimed it had notified Gilead of this situation in 2013. Gilead, on the other hand, claimed Merck's patents weren't applicable, because they failed to specify a disease that the compounds in question treated.[232]

[232] Rory Carroll and Andrew Chung, “Gilead Ordered to Pay Merck $200 Million in Hepatitis C Drug Patent Dispute - Reuters,” March 24, 2016, https://www.reuters.com/article/us-gilead-sciences-merck-co-damages/gilead-ordered-to-pay-merck-200-million-in-hepatitis-c-drug-patent-dispute-idUSKCN0WR00V; Reuters, “Merck Wins Hepatitis C Drug Patent Claim Against Gilead,” *The New York Times*, March 22,

Once again, the real story was more complicated. Gilead and Merck had briefly flirted with the idea of a collaboration, and the series of events the court documents reconstructed went something like this.

In 2001, Merck filed a number of patents on compounds related to what would eventually become sofosbuvir. Reviewing these patents once they were made public, Pharmasset assigned one of its chemists, Jeremy Clark, to attempt to create and refine a direct acting antiviral based on them. Clark succeeded, filing a patent on a modified version (PSI 6130) of one of these compounds in 2003.[233] PSI-6130, you may recall, was a precursor to sofosbuvir.

Around this time, Pharmasset and Merck were looking to launch a collaboration focused on Hepatitis C direct acting antivirals. The companies set up a 'firewall' to ensure no patent infringement would take place. No one involved in the collaboration would be involved with either company's efforts to file and defend its own patents. This would allow the sharing of the structures of the compounds, so each company could determine if the other's product was promising. Under these conditions, Pharmasset shared the structure of Clark's invention, PSI-6130. PSI-6130 may have been based on Merck's early patents, but it was different enough that it seemed like a more promising version of the compound than Merck's own.[234]

Dr. Phillipe Durette, one of Merck's researchers, participated in the call during which PSI-6130 was discussed. Durette was both a chemist and a patent attorney. Under

---

2016, sec. Business, https://www.nytimes.com/2016/03/23/business/merck-wins-hepatitis-c-drug-patent-claim-against-gilead.html.

[233] Gilead Sciences, INC. v. Merck & Co. INC., Merck Sharp & Dohme Corp., Ionis Pharmaceuticals, INC. (United States District Court for the Northern District of California April 25, 2018).

[234] Gilead Sciences, INC. v. Merck & Co. INC., Merck Sharp & Dohme Corp., Ionis Pharmaceuticals, INC.

the terms of the firewall, he shouldn't have been on that call, because he was working on two of Merck's patents for Hepatitis C direct acting antivirals, relatives of the ones from whose patents Clark had drawn his inspiration. Shortly after the call, Merck removed Durette from the collaboration team and left him to continue working on the patent team. Durette later modified the patents to include Merck's version of PSI-6130.[235]

This led to the suit with Merck claiming that Gilead's marketing of sofosbuvir and ledipasvir violated their patent on a similar substance. Merck won the first suit. But as the appeals process progressed, the involvement of Durette on that call, and in filing the patents Merck claimed were infringed, came to light. The court returned a verdict of "unclean hands". Regardless of whether or not Gilead had done what Merck had accused it of doing, the court judged Merck's misconduct to be so severe as to irrevocably taint any court rulings in their favor. This finding of unclean hands was due both to the violation of the firewall, and because Durette lied under oath, claiming that he had not participated in the meeting in question at all. Merck tried to appeal the case. It failed; the federal circuit court to which it was appealed agreed with the findings of the lower court. Merck's behavior had made its patent unenforceable, no matter to whom the intellectual property belonged.[236]

Merck wasn't the first entity to sue Gilead or Pharmasset over sofosbuvir. Jeremy Clark, the inventor on that first patent, beat them to it. But he had even less success.

---

[235] Gilead Sciences, INC. v. Merck & Co. INC., Merck Sharp & Dohme Corp., Ionis Pharmaceuticals, INC.
[236] Gilead Sciences, INC. v. Merck & Co. INC., Merck Sharp & Dohme Corp., Ionis Pharmaceuticals, INC.; "Merck Hepatitis C Virus Treatment Patents Unenforceable Due to Unclean Hands," *IPWatchdog.Com | Patents & Patent Law* (blog), May 7, 2018, http://www.ipwatchdog.com/2018/05/07/merck-hcv-treatment-patents-unenforceable/id=96509/; "Merck Loses Bid to Revive $200 Million Gilead Verdict at U.S. High...," *Reuters*, January 7, 2019, https://www.reuters.com/article/us-usa-court-merck-idUSKCN1P11G5.

Clark's first suit was in 2008. He had left Pharmasset in 2007, seeking a new research position, but when Pharmasset became publicly traded, he wanted a cut of the profits. He claimed it was his prodrug that gave the little startup its value.[237]

Unfortunately for Jeremy Clark, he'd signed an employment contract that gave all the intellectual property rights of the compounds he invented to Pharmasset. It also mandated binding arbitration to settle all disputes. The case was thrown out of court.[238]

Undaunted, Clark sued again, this time directly suing Schinazi, then Schinazi, the VA, and Emory. Because of the binding arbitration clause, all his suits were unsuccessful.[239] When 2013 rolled around and sofosbuvir was FDA approved, it was Michael Sofia and his 'trojan horse' who enjoyed the spotlight. Clark was a footnote at best.

The intellectual property woes weren't confined to disgruntled former employees and angry competitors. The US Federal Government was another player. The legal issue here centered on one deceptively simple question: where had the money to fund the development of sofosbuvir originated?

There are a lot of ways scientists, particularly in the pharmaceutical industry, can get money. One of the most prominent is the federal government, which, through the National Institutes of Health, disburses approximately 40.3 billion dollars annually. Over 80% goes to independent research entities, like universities and medical schools, 10% to

---

[237] Jeremy Clark, Civil Action No. 08-S-0204-NE (UNITED STATES DISTRICT COURT NORTHERN DISTRICT OF ALABAMA NORTHEASTERN DIVISION December 7, 2008).
[238] Clark.
[239] Jeremy Clark, CASE NO. 5:09-cv-1789-SLB (UNITED STATES DISTRICT COURT NORTHERN DISTRICT OF ALABAMA NORTHEASTERN DIVISION September 7, 2010); Clark, Civil Action No. 08-S-0204-NE; Jeremy Clark, Civil Action Number 5:10-cv-01487-AKK (UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ALABAMA NORTHEASTERN DIVISION December 20, 2010).

NIH's own laboratories.[240] But this money comes with strings attached. The source of that federal money needs to be acknowledged on the patent. And that patented substance has to be available to the US federal government, so the federal government can use it for its purposes without unreasonable barriers. This could cover entities like Medicare and the VA, but is never enforced.

Both the right of inventors to patent federally-funded innovations, and their attendant responsibilities, are due to the Bayh-Dole Act of 1980, which we have touched on.

Under Bayh-Dole, researchers may hold patents on inventions based on federally funded research. But these patentholders, whether they are universities or companies, have to make sure that the invention is available at reasonable terms to fulfill the needs of the federal government, and they have to disclose, on the patent, that federal funding was received for the project. If the patentholder fails to provide the invention to the federal government in a way that can fulfill the needs of the government—or in a way that doesn't address health and safety needs, the federal government may use what are called "march-in" rights whereby it may license an invention to a company or entity that will provide the invention to supply the government's needs. If the patentholder fails to disclose federal funding for the invention on the patent, the federal government can impose a number of penalties, including assuming the intellectual property rights of the invention for itself or revoke the patent.

[240] National Institutes of Health, "Budget | National Institutes of Health (NIH)," National Institutes of Health (NIH), June 29, 2020, https://www.nih.gov/about-nih/what-we-do/budget.

Both of these stipulations are seldom enforced. The assumption is that the needs of federal programs are being met until it's demonstrated that they're not. This means that march in rights have never been invoked. NIH has been lax on enforcing the disclosure of public funding on patents, and has not used is government-use or march-in authorities for drugs.[241]

Furthermore, Bayh-Dole's march-in process was designed to be difficult for the federal government to invoke. The language of the law is fairly straightforward, but the administrative process required to actually use march-in is not. Its use as a price-control mechanism has been hotly debated by policy researchers, and the NIH itself has declined to use it to lower prices. Its use in emergencies, such as when a company fails to produce a drug that patients with a rare disease rely on, is hampered by this lengthy process. Indeed, when march-in was invoked in 2013 in just such a case, the NIH declined to use the process twice. The case in question was a shortage in agalsidase beta, a treatment for Fabry disease. Fabry disease is a condition in which the body cannot produce the enzyme needed to break down certain fats, and patients need supplemental treatments with agalsidase beta (Fabrazyme) to stave off painful and potentially fatal buildups of these fats. In 2009, a contamination at the manufacturer that produced Fabrazyme led to a halt in production. The NIH declined to march-in, despite Fabrazyme being a federally funded invention. The first refusal was because NIH believed that the original company,

[241] William O'Brien, "March-in Rights under the Bayh-Dole Act: The NIH's Paper Tiger," *Seton Hall Law Review* 43 (2013): 1403; Amy Kapczynski and Aaron S. Kesselheim, "'Government Patent Use': A Legal Approach To Reducing Drug Spending," *Health Affairs* 35, no. 5 (May 1, 2016): 791–97, https://doi.org/10.1377/hlthaff.2015.1120; Hannah Brennan et al., "A Prescription for Excessive Drug Pricing: Leveraging Government Patent Use for Health," *Yale Journal of Law and Technology* 18, no. 1 (April 2, 2017), https://digitalcommons.law.yale.edu/yjolt/vol18/iss1/7.

Genzyme, would begin production before a new company could get their facilities ready to produce the treatment, and the second, when Genzyme failed to resume production within the estimated timeframe, claimed that it was inappropriate to invoke march-in without a second company having applied for a license and standing by ready to begin production of the patented substance.[242]

The second refusal is, on examination, difficult to justify. It would require another company to have infringed the patent on the treatment before being assured that their infringement would be protected by the march-in process. No company would take such a risk, and NIH's judgement in that case raised the bar for invoking march-in to an impossible height. Until this part of the Bayh-Dole Act is reformed, using march-in to address misbehaviors of federally-funded patentholders is unlikely.[243]

The other responsibility a federally-funded patentholder has under the Bayh-Dole Act is to disclose whether they received federal funding on the patent itself. This is similarly difficult to enforce. This difficulty is thanks to the confidential nature of the federal database of funding and patents, iEdison. The strict rules keeping iEdison confidential, and the resulting lack of comprehensive information about who received funding for what, shut out researchers seeking to determine if underreporting of federal funding on patents is a systemic problem.[244] We can, however, work backwards, comparing databases like NIH's REporter with publications and patents.

---

[242] William O'Brien, "March-in Rights under the Bayh-Dole Act: The NIH's Paper Tiger," *Seton Hall Law Review* 43 (2013): 1403.
[243] O'Brien.
[244] Arti Rai and Bhaven Sampat, "Accountability in Patenting of Federally Funded Research," *Nature Biotechnology* 30, no. 10 (January 1, 2012): 953–56.

Bayh-Dole's applicability only to federally-funded inventions, and the reluctance to enforce its provisions, make it an unlikely candidate as a solution to high drug prices. Nevertheless, the interest in Bayh-Dole as a potential remedy for high drug costs has extended to sofosbuvir, and there's considerable interest in where, exactly, the funding used to develop sofosbuvir came from. Sofosbuvir did indeed see some federal funding. Pharmasset received a grant through the Internal Revenue Service for $244,479.25 under the Qualifying Therapeutic Discovery Project Grants program for its research on sofosbuvir between 2008 and 2011.[245] Other researchers have been interested in whether Pharmasset received any other federal funding for its work on sofosbuvir.

In early 2018, researchers at Knowledge Ecology International, a thinktank focused on intellectual property and accountability, found grant records that raised questions about the history of sofosbuvir.[246] A search of the National Institutes of Health grants database showed that several of the authors of the 2010 revision of the patent had received federal funding on research related to Hepatitis C direct acting antivirals and nucleoside analogues. KEI published a blistering letter to Health and Human Services (HHS) demanding action.[247]

HHS never replied to the letter. After reading KEI's official announcement, I crosschecked the NIH grant database against the lists of authors on other sofosbuvir-related patents and papers, and found that many—if not most—of the researchers listed on those papers and patents were receiving funding for Hepatitis C direct acting antiviral

[245] The Price of Sovaldi and its Impact on the United States Health Care System.
[246] "About KEI," *Knowledge Ecology International* (blog), November 24, 2018, https://www.keionline.org/about.
[247] Knowledge Ecology International, "U.S. Patent 7,964,580," 2018.

research. Yet, not only were none of the compounds that got funding sofosbuvir, not one of them was a substance that Pharmasset or Gilead ever brought to market. (See Appendix 1).

Most interesting of all the federal grants were the ones granted to people who *weren't* Pharmasset employees. These individuals worked at academic institutions, with grants to study direct acting antivirals for Hepatitis C. They didn't appear on the patents for sofosbuvir, but they *did* appear on the publications concerning sofosbuvir for an academic audience. Their involvement was often in things like testing the drugs in the laboratory and verifying Pharmasset's findings. While these do not qualify researchers to be inventors on the patent, Bayh-Dole also applies to the process of reducing to practice—in this case, making the drug usable for patients.[248] The involvement of grant money from these researchers, even though they weren't on the patents, could have been enough to make Bayh-Dole applicable.

Pharmasset was a small company with a tight budget.[249] As a cost-saving measure, Pharmasset had approached at least one laboratory that was federally funded, with which members of the research team were already familiar. They then asked this laboratories to run specific tests that were otherwise expensive to conduct. The laboratory would use federal funding to do so, as those tests fell within the purview of their existing NIH grant. Sometimes, companies would give the academic laboratories grants to pay expenses. At other times, academic laboratories simply used their own funding to complete the process. I was informed that this is a common practice.[250]

[248] "Exercise of March-in Rights," 37 CFR § 201e (2002).
[249] Interview with HCV Researcher.
[250] Interview with HCV Researcher.

If it is, it means that the pharmaceutical industry is accessing federal funds via academic laboratories, and then patenting the research and profiting from it without attribution. The academic laboratories in the case of sofosbuvir were not listed on the patent, and probably did not see any of the profit. It would also explain why there were so many researchers with federal grants related to other direct acting antivirals listed on the publications about sofosbuvir. (See Appendix 1).

Furthermore, the precedent established by NIH make those rights almost impossible to invoke. Congressional action to remove barriers to invoking march-in and oversight to make sure that it is used in alignment with the statute will be necessary before the provisions of Bayh-Dole intended to protect the taxpayer are usable.

Indeed, Louisiana's proposal to use §1498 to access Hepatitis C medications is a far more feasible one. §1498 has considerable precedent, including in the pharmaceutical realm. The lapse in its usage is more due to a lack of political will than the difficulty of applying the law.

If we do not use these policy tools, there are other interventions available to us. One of these is the program created by the Ryan White Act, which provides care to HIV/AIDS patients in community settings.

CHAPTER 12

RYAN WHITE AND THE LESSONS OF AIDS

Outside of patent law options, what other tools are available to increase Hepatitis C treatment? One model is in use for HIV/AIDS. There are a lot of similarities between HIV/AIDS and Hepatitis C. They're transmitted in many of the same ways, and both are stigmatized. In many of the responses to Hepatitis C in the United States, we've demonstrated that we haven't learned the lessons of the AIDS epidemic. But the ways in which we confronted that epidemic, and the systems and organizations that helped HIV patients are in many respects still with us. Some of these AIDS policies could help with Hepatitis C if we emulated them.

HIV/AIDS and Hepatitis C often occur at the same time in the same patient. Both can be acquired through sharing needles, or other blood to blood contact. This is one of the reasons that direct acting antivirals, like sofosbuvir, are so important in the treatment of Hepatitis C. Combination therapy doesn't work well in HIV-infected patients.[251]

There were many lessons we should have learned from the HIV epidemic that are now highlighted by the similarities between the two diseases. Both diseases prey on vulnerable populations, including people who inject drugs. Both are associated with stigma because of the ways they can be spread—HIV because of its association with sex, Hepatitis C because of its association with injection drug use. And in both cases, patients have struggled to access the drugs they need to control or treat the disease.

[251] Manish Patel et al., "Highly Successful Hepatitis C Virus (HCV) Treatment Outcomes in Human Immunodeficiency Virus/HCV-Coinfected Patients at a Large, Urban, Ryan White Clinic," *Open Forum Infectious Diseases* 4, no. 2 (April 5, 2017), https://doi.org/10.1093/ofid/ofx062.

HIV first emerged in the 1980s with a spate of rare cancers and fungal pneumonias among young gay men in the San Francisco Bay Area and in New York. What began as a scattering of odd fatalities became a devastating epidemic of an incurable, fatal disease, immediately and deeply associated with a fledgling queer community that had just begun to fight for recognition, acceptance, and respect. It was a devastating blow.

It's a legacy that younger generations of the queer community are still grappling with—even if some of us are unaware of how it's shaped our community. I, personally, did not come to terms with it until I was in the early stages of researching this book, on a trip to Washington D.C. During the course of a day wandering the Capitol Mall, something I'd never been able to do free from the supervision of a high school chaperone, I visited the Smithsonian National Museum of Natural History, which had an exhibit on infectious disease.

Coming face-to-face with the pictures of hospital beds and patients, familiar California hills the backdrop to suffering, courage, and horror alike, drove home the reality in a way no amount of reading had. The HIV/AIDS epidemic happened a few short years before I was born. My mentors, family members, elders in the queer community lived through this. They lived *with* this. My generation, even if we didn't know it, lived with this. How many more voices would we have to learn from, to guide us, had they not been silenced so young by AIDS?

The Reagan Administration dragged its feet in responding to AIDS. Suspicion fell on prejudice as the reason. No one seemed to care about what happened to gay men. The community banded together, creating a wave of activism that would influence later

patient activists, including the breast cancer community's efforts to access clinical trials.[252] AIDS activists protested for greater access to treatment. They protested for better protection. For acceptance. For the tens of thousands of dead, represented in a quilt that stretched down the very Capitol Mall I'd strolled through that afternoon. That, too, was the legacy of AIDS and of the queer community.[253]

AIDS was devastating to the queer community. But it didn't stay there. As diseases do, it trickled into the poorest, most vulnerable parts of society worldwide, and there it stays. Now, its major association in the United States is with drug use, like Hepatitis C. And it can be vertically transmitted, from mother to child in the womb. In Africa, because of lack of access to treatment, it is devastating. In the United States, the drugs needed to manage it and guarantee the patient a lifespan not noticeably different from their peers are widely available. They are covered by Medicare and Medicaid and private insurance… and also, for those who qualify for none of those, by the Ryan White Act.

Ryan White was 13 when he was diagnosed with AIDS. A hemophiliac, he had been infected by a blood transfusion from a donor with the disease. Despite his diagnosis, he wanted to continue to attend school, but the pervasive fear and misinformation about the disease meant that he and his family had to engage in a series of legal battles to allow him to attend public school. A paper published early in the epidemic had claimed that HIV/AIDS could be spread by "common household contact" and despite it being

---

[252] Steven Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge*, 1st ed. (Berkeley and Los Angeles, California: University of California Press, 1998), https://www.ucpress.edu/book/9780520214453/impure-science.

[253] Randy Shilts, *And the Band Played on : Politics, People, and the AIDS Epidemic* (New York: St. Martin's Press, 1987).

debunked, the fear lingered. Ryan White continued to advocate for HIV/AIDS education until his death in 1990, the year that the act that bears his name was signed into law.[254]

The Ryan White Act has been reauthorized repeatedly since then, changing with our understanding of the disease and the needs of the communities combatting it. It fills a gap in the health system. Medicaid provides HIV/AIDS treatment for those patients who qualify for it, and is the largest provider of treatment. Medicare comes second. The Ryan White Act covers people who aren't able to get their medications in any other way. It differs from traditional insurance in being a program of grants.[255]

Cities were particularly hard hit by the AIDS epidemic in the 1980s. The earliest forms of the Ryan White program came in the form of federally funded programs providing care and medications for patients in the most heavily affected cities. These "demonstration" programs formed a framework that then guided the formation of the programs funded by the Ryan White Act. In its present form, the Ryan White Act provides emergency grants to states, cities, and community providers.

It's not just medication that the Act provides; it's a holistic approach that also covers substance abuse treatment, mental health services, and other services, all aimed at increasing the efficacy of treatment for and the health of families and individuals with the disease.

Treating patients for Hepatitis C isn't new to the clinics established and supported by the Ryan White Act. Hepatitis C has been a common coinfection with HIV, especially

[254] Health Resources & Services Administration, “Who Was Ryan White?,” Text, HRSA Ryan White HIV/AIDS Program, August 9, 2016, https://hab.hrsa.gov/about-ryan-white-hivaids-program/who-was-ryan-white.
[255] Jessamyn Taylor, “Caring for" Ryan White": The Fundamentals of HIV/AIDS Treatment Policy,” 2005.

in people engaging in injection drug use. The diseases have the same route of transmission. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that about 25% of people with HIV also have Hepatitis C. Worldwide, 2.3 million people are thought to have both diseases.[256] Not only are there a lot of coinfected patients, but the disease progresses faster for them with significantly worse outcomes. The full progression of Hepatitis C can take up to 25 years in someone who doesn't have HIV/AIDS. It can take less than 5 years for someone who has both diseases.[257]

This didn't mean that providers at HIV clinics were eager to start Hepatitis C treatment for their patients. There were a lot of complications. Prior to the arrival of DAAs, Genotype 1 of Hepatitis C was one of the least responsive to combination therapy. It was also one of the most common genotypes in the United States. If a patient with Genotype 1 only had mild liver damage, providers often recommended that they wait for treatment.[258]

These structures were still in place in 2013, once direct acting antiviral regimens became available. They were also still necessary. Patients attending Ryan White-funded clinics receive their medical care from a variety of sources. Some are uninsured. Some are on Medicaid or Medicare, and some have private insurance. This meant that whether or not a diagnosed patient could then access medication depended on their insurance.

---

[256] Patel et al., "Highly Successful Hepatitis C Virus (HCV) Treatment Outcomes in Human Immunodeficiency Virus/HCV-Coinfected Patients at a Large, Urban, Ryan White Clinic."
[257] Swan and HIV/AIDS Bureau., *Care and Treatment for Hepatitis C and HIV Coinfection: Expanding Access Though the Ryan White CARE Act*.
[258] "The Price of Solvaldi and Its Impact on the United States Health Care System," § COMMITTEE ON FINANCE UNITED STATES SENATE (2015).

Some uninsured patients are able to qualify for cost reduction programs through the manufacturers, but this is by no means a reliable system of drug delivery.[259]

Exacerbating the situation is the sheer time and effort it takes for a patient to initiate Hepatitis C treatment. This usually consists of multiple visits, invasive and painful procedures, and long waits for approval. Clinics that can offer most of these services, such as ultrasounds so biopsies can be performed on site, decrease these hurdles.[260] This is a model for Hepatitis C already piloted by the Ryan White Act and the clinics it funds.

The Ryan White Act is now funded through annual appropriations.[261] Given the high prevalence of HIV and Hepatitis C coinfection, dedicating further funds to obtain Hepatitis C treatment for coinfected patients is a promising tactic. The infrastructure to deliver treatment effectively already exists.

The United States hasn't been alone in struggling to create a framework with which to confront Hepatitis C. Indeed, the Americas account for only a fraction of global Hepatitis C infections. Other countries found affording sofosbuvir-based regimens difficult, and the ways in which they have responded demonstrate a number of strategies which may be deployed to broaden Hepatitis C treatment in the United States as well.

---

[259] Rebecca Cope et al., "Treating Hepatitis C in a Ryan White-Funded HIV Clinic: Has the Treatment Uptake Improved in the Interferon-Free Directly Active Antiviral Era?," *AIDS Patient Care & STDs* 30, no. 2 (February 2016): 51–55, https://doi.org/10.1089/apc.2015.0222.
[260] Swan and HIV/AIDS Bureau., *Care and Treatment for Hepatitis C and HIV Coinfection: Expanding Access Though the Ryan White CARE Act*.
[261] "The Ryan White HIV/AIDS Program: The Basics," The Henry J. Kaiser Family Foundation| HIV/AIDS, February 4, 2019, https://www.kff.org/hivaids/fact-sheet/the-ryan-white-hivaids-program-the-basics/.

CHAPTER 13

SOFOSBUVIR ON THE GLOBAL STAGE

The United States wasn't the only country struggling to contain Hepatitis C. All over the world, other countries had the same, or similar problems, some at an even larger scale. Sofosbuvir forms the backbone of many treatment regimens for Hepatitis C, and its high price meant that governments around the world had to scramble to figure out how they were going to treat all their patients.

Viral Hepatitis tends to be lumped together in global health statistics, even if hepatitis can be caused by many different viruses, not all of which are related. The major hepatitis viruses are Hepatitis A, Hepatitis B, and Hepatitis C. Hepatitis D and E are two other viruses, but their impacts are minor compared to those of Hepatitis B and C.

Hepatitis A is an acute illness, meaning that the patient gets it, becomes extremely ill, and then either dies or recovers. It caused about 11,000 deaths in 2015, less than one percent of hepatitis deaths worldwide. Unlike Hepatitis B or C, it spreads through food and water contaminated by feces.[262] This was the driving force behind the 2017 outbreak in Los Angeles. Los Angeles has a large homeless population, and a lack of toilets for them to use. As a result, people had nowhere to relieve themselves but the street. This caused a serious outbreak, more evidence that public health is inextricably linked to public welfare.[263]

---

[262] World Health Organization, "Global Hepatitis Report, 2017" (World Health Organization, 2017), http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1.

[263] Los Angeles Department of Public Health, "Hepatitis A Outbreak in Los Angeles County," September 19, 2017, http://publichealth.lacounty.gov/acd/Diseases/HepA.htm.

The good news about Hepatitis A is that there is an extremely effective and safe vaccine for the disease, and this has been a major advance in controlling it.[264]

Unlike Hepatitis A, Hepatitis B is a virus transmitted by infected blood. It affects 257 million people around the world. Unlike Hepatitis C, there are few effective treatments for it. Treatment usually consists of interferon and some direct acting antivirals, but they're not very effective and they're a lot harder to tolerate than the direct acting antivirals for Hepatitis C. Many of the people involved in the development of direct acting antivirals for Hepatitis C are now working on treatments for Hepatitis B, though, from remarks I overheard at the conference I attended in December of 2019, even the researchers who spearheaded the development of sofosbuvir seem to find *reducing* rather than eliminating the virus in a patient to be a more practical goal.

The good news about Hepatitis B is that vaccination is possible, and already having an impact. Babies are now vaccinated within hours of birth. This has vastly reduced rates of infection. Like Hepatitis C, Hepatitis B can be passed from mother to child, and makes this leap even more often than Hepatitis C does. Hepatitis B, like Hepatitis C, can become a chronic infection, slowly progressing over years or even decades. Because of the ways it's transmitted, it often infects people who also have HIV, leading to similar challenges as HIV/Hepatitis C coinfection. It also leaves the patient open to being infected by Hepatitis D, a virus that requires a previous Hepatitis B infection in order to infect a human host.[265] This is because Hepatitis D is something called an "incomplete virus" and needs Hepatitis B's genetic code to replicate

[264] World Health Organization, “Global Hepatitis Report, 2017.”
[265] World Health Organization.

successfully. People with both diseases get a lot sicker than those with just Hepatitis B, and having Hepatitis D makes the already questionably effective treatments possible for Hepatitis B even less likely to work. But because it needs Hepatitis B to infect people, Hepatitis D can be prevented by preventing or treating Hepatitis B.[266]

Hepatitis E, like Hepatitis A, is transmitted by contaminated water. It causes more deaths than Hepatitis A, especially among pregnant women, but is usually an acute illness, an illness that's brief and the patient either dies or clears it from their body within a relatively short time. There is one vaccine approved in China, though it's pending approval in other countries.[267]

All these diseases put together are the 'viral hepatitis' pandemic—a pandemic that kills more people worldwide than even HIV/AIDS. Hepatitis C accounts for about 71 million hepatitis patients worldwide.[268]

There are two major ways that Hepatitis C spreads. One of them, injection drug use, we've already discussed. Prevalence in the US doubled between 2010 and 2014 because of increasing injection drug use, and the other place this happened was Europe. Europe has a much higher incidence of the disease than the Americas do. About 62 people per every 100,000 people in Europe have Hepatitis C, largely due to injection drug use. In the Americas, it's about 6 people per every 100,000.

Another hard-hit region is the Eastern Mediterranean region, including Egypt and other North African countries, Iran, Iraq, Afganistan, Pakistan, Saudi Arabia, Ethiopia, and the Gulf States. Here, almost 63 people per 100,000 live with the disease. The driver

[266] World Health Organization.
[267] World Health Organization.
[268] World Health Organization.

of these high numbers of patients isn't drug use. It's unsafe healthcare procedures. In countries with poor health infrastructure, often because of unrest and systemic poverty, it can be difficult to obtain a steady supply of clean needles, let alone test blood products or donor organs. This makes it very easy for patients to be exposed to contaminated blood when they undergo routine medical procedures. So far, there's been a lot of focus on prevention, including the invention of needles that can only be used once, rendering reuse impossible.

This has seen some success, driving the number of new infections down. But since Hepatitis C can linger for years to decades before patients become symptomatic, many of these countries are seeing high infection rates due to healthcare practices in the 1960s and 1970s. For example, the government of Egypt launched health initiative to control schistosomiasis in the 1950s. Schistosomiasis is a parasitic disease, the treatment for which was administered by injection. The initiative was extremely effective in its original aim, but the reuse of needles had the unintended effect of spreading Hepatitis C through the populations receiving treatment. This gave Egypt a remarkably high prevalence of Hepatitis C, and all because of its successful public health intervention against schistosomiasis![269]

The most important aspect of control is prevention. This isn't just because of the high costs of direct acting antivirals. It's also due to the difficulty of testing patients. Hepatitis C has to be diagnosed through laboratory tests that detect the virus. Right now, only about 20% of patients with the disease are tested and diagnosed. Prevention has had

[269] G. Thomas Strickland, "Liver Disease in Egypt: Hepatitis C Superseded Schistosomiasis as a Result of Iatrogenic and Biological Factors," *Hepatology (Baltimore, Md.)* 43, no. 5 (May 2006): 915–22, https://doi.org/10.1002/hep.21173.

a significant impact already, driving down infection rates. The World Health Organization hopes to expand that in a variety of ways, including increasing screening of blood donations and decreasing needle reuse. The biggest challenge is harm reduction for people who inject drugs. A major way to do this is to distribute syringe and needle sets to people who inject drugs to prevent transmission through reuse of those materials. WHO has a separate goal for that: an average 300 sets for each individual per year by 2030. The current average is 27.

The next step is diagnosis. Diagnosis is difficult because of how long Hepatitis C can survive in the body before showing symptoms. Even without symptoms, a Hepatitis C patient can still spread the disease. Since many of the symptoms arise because of the damage the disease does to the liver, they're also nonspecific. Someone looking at the patient might not know the patient is infected without a laboratory test for the genetic material of the virus. Currently, in low income countries, only about 8% of estimated Hepatitis C cases have been diagnosed. In high income countries, that number is about 43%. The World Health Organization hopes to increase the number of people screened for Hepatitis C and diagnosed from 20% to 90% by 2030. Worldwide, access to diagnostic tests has increased as costs have come down for the initial tests, some of which cost as little as $1. But these tests sometimes require confirmation, and the more thorough tests can cost a great deal more than $1—anything from $15 - $100, which many of the people most vulnerable to the disease simply can't afford. Figuring out how to bring down these costs, and test more people in the first place, must be priorities.[270]

[270] World Health Organization, “Global Report on Access to Hepatitis c Treatment: Focus on Overcoming Barriers.”

After diagnosis, another barrier arises: fewer than 7% of those people diagnosed with Hepatitis C actually start treatment. Hepatitis C has the advantage that it can be treated with a single short course of therapy, but the treatment barriers that US patients face are repeated worldwide. The WHO has set a goal of treating 80% of diagnosed patients by 2030. Currently, member nations are not on track to meet that goal.

There is some good news. Despite these barriers, 1.76 million people were able to get treated in 2016 alone. This was an increase of almost half a million from the year before. But those 1.76 million people were concentrated in a handful of countries that took particularly aggressive action in confronting their Hepatitis C outbreaks. For example, Egypt alone accounted for about 40% of all people who accessed treatment in 2016, thanks to its Hepatitis C elimination campaign. This patchwork derives from two major factors; governmental involvement, and access to the medications.[271]

Unsurprisingly, price plays a role in creating these international barriers as well as the ones faced by patients in the United States. When sofosbuvir appeared on the scene, it was already evident that low income countries hard-hit by the disease would be flatly incapable of paying the prices the drug was being sold for in the US and Europe. To compensate for this, and presumably, the bad publicity it would cause, Gilead engaged in a practice known as 'voluntary licensing'. Voluntary licensing is when a company allows its products to be produced by a manufacturer or group of manufacturers for a much lower price for a specific market. In the case of Gilead, it entered an agreement with 11 manufacturers in India to produce sofosbuvir for a list of 100 low income countries for less than $100 per course of treatment.

[271] World Health Organization.

In some cases, this was a success. The World Health Organization estimates that about 75% of Hepatitis C patients live in low- and middle-income countries, and this initiative, theoretically, should have lowered access barriers for those countries.

But Gilead's voluntary licensing only covered those 100 countries. For middle income countries, like China and Brazil, access was still a serious challenge. Without the discounts, affording treatments for their needy populations was extremely difficult. These countries were stuck without the money of high-income countries to make treatments available, but weren't poor enough to qualify for discounts.

As a result, many took to the courts.

Both China and Brazil have now refused to grant Gilead patents for sofosbuvir in their countries because of the high price of the drug. By refusing to recognize these patents, both countries are giving themselves permission to manufacture the compound for their needs, an *in*voluntary licensing, much as USC§1498 allows the US government to do, only these countries aren't hesitating to use it. The court battles have dragged on.

In Brazil, early court rulings were against Gilead. Brazil didn't grant the company a patent, and as a result the price stayed fairly low, at about $16 in US dollars per course of treatment. But the government's position changed in January of 2019. The patent was, at last, granted. As a result, the price of sofosbuvir increased to about $240 USD per course of treatment. It's much cheaper than the price of the drug in the United States, but it's likely the resulting access issues will impede the government's aim of Hepatitis C elimination in the country.[272]

[272] Patricia Campos Mello, "Cost of Hepatitis C Drug Price Skyrockets 1,422% after Patent Approval," *Folha de S.Paulo*, October 22, 2019,

Another 'in the middle' issue is produced by income disparities in middle- and high- income countries like the United States, where insured subpopulations enjoy easy access to the drug, and uninsured subpopulations do not. This is one of the areas that WHO identifies as a particular challenge in reaching its goal of elimination by 2030. These countries don't qualify for discounts, but they do have populations that aren't receiving the drugs.

Pushback against pricing on the global stage is if anything stronger than that within the US. Many international aid and health groups are strongly invested in eliminating Hepatitis C. Pricing is seen as the primary barrier to realizing that goal. Médecins Sans Frontières (Doctors Without Borders) is an international medical aid group that has been at the forefront of the fight to obtain medications for populations that can't otherwise afford them.

MSF's work expands beyond treatments for Hepatitis C. Using the World Trade Organization's Trade-Related Aspects of International Property Rights (TRIPS) agreement, it has attempted to encourage the use of compulsory licenses for patented materials. Compulsory licenses mean that a company or other entity is producing or using a patented material without the permission of the patent holder.

MSF justifies this by pointing out that people worldwide struggle to afford the medicines they need to survive, and that one of the aims of TRIPS is to ensure that intellectual property rights don't outweigh public health needs.[273] TRIPS is a treaty that

---

https://www1.folha.uol.com.br/internacional/en/scienceandhealth/2019/10/cost-of-hepatitis-c-drug-price-skyrockets-1422-after-patent-approval.shtml.

[273] "MSF: USTR Special 301 Report Calls Out Countries for Protecting Public Health," Doctors Without Borders - USA, April 27, 2018, https://www.doctorswithoutborders.org/what-we-do/news-stories/news/msf-ustr-special-301-report-calls-out-countries-protecting-public.

seeks to protect intellectual property worldwide. Its section on patents specifically requires countries to protect, via patents, new inventions. The granting of patents for pharmaceutical products is a fairly recent practice in most of the world. Prior to the 1970s, only the United States, the United Kingdom, West Germany and France granted patents to pharmaceutical inventions. The practice spread in the 1980s and 1990s, and TRIPS made it universal.[274]

What a new invention is can sometimes be controversial. The practice of 'evergreening' patents, for example, involves making a small change that's debatable in its efficacy to re-patent an invention whose patent is about to expire. TRIPS specifically requires inventions to "involve an inventive step" and to be industrially applicable. However, there are some circumstances that allow a government to refuse to issue a patent. Things a government deems dangerous to either public order or morality can have their patents refused, and "diagnostic, therapeutic and surgical methods" can also be left unpatented. Furthermore, TRIPS includes what are called "flexibilities" to address public health needs.[275]

These "flexibilities" allow a TRIPS signatory to use a compulsory license to make a medication available for domestic use or to be exported to another country in need. They are reserved for health emergencies or “circumstances of extreme urgency”, which

[274] Kenneth C. Shadlen, Bhaven N. Sampat, and Amy Kapczynski, “Patents, Trade and Medicines: Past, Present and Future,” *Review of International Political Economy* 27, no. 1 (January 2, 2020): 75–97, https://doi.org/10.1080/09692290.2019.1624295.
[275] World Trade Organization, “WTO | Understanding the WTO - Intellectual Property: Protection and Enforcement,” World Trade Organization, accessed January 28, 2020, https://www.wto.org/english/thewto_e/whatis_e/tif_e/agrm7_e.htm.

can include “HIV/AIDS, tuberculosis, and malaria”. Furthermore, a section of the treaty allows medications to be made under a compulsory license and exported.[276]

To this end, MSF has launched a series of legal challenges in countries around the world, aiming to encourage the use of compulsory licensing. This doesn't just target low income countries. A 2018 effort in Europe highlighted low access within the European Union as a reason to revoke Gilead's sofosbuvir patents in the European Union. Though MSF joined forces with a number of other organizations, the first court upheld Gilead's intellectual property rights. MSF and its allies appealed the decision.[277]

A similar court case is ongoing in China. There, MSF is arguing that velpatasvir, a drug often combined with sofosbuvir in order to treat Hepatitis C, doesn't merit a patent in the first place under China's patent laws. The motivation is access, with an extra tinge of injustice, as China is a major source for the raw materials needed to create medications. Perfectly capable of manufacturing enough of the drug to fulfill the needs of its citizens, China instead is hobbled by these patents making it impossible for most Hepatitis C patients to access it. According to MSF, interferon treatment, despite all its side effects, is still used in China because of the expense of direct acting antivirals like velpatasvir.[278] However, China did invalidate the patent for sofosbuvir in 2018.[279]

---

[276] World Trade Organization, “WTO | Intellectual Property (TRIPS) - TRIPS and Public Health,” World Trade Organization, accessed January 28, 2020, https://www.wto.org/english/tratop_e/trips_e/pharmpatent_e.htm.
[277] “Appeal Lodged against Decision to Uphold Gilead’s Patent on Hepatitis C Drug | MSF,” Médecins Sans Frontières (MSF) International, accessed January 26, 2020, https://www.msf.org/appeal-lodged-against-decision-uphold-gilead%E2%80%99s-patent-hepatitis-c-drug.
[278] “MSF Challenges Gilead’s Undeserved Patent on Hepatitis C Drug in China,” Doctors Without Borders - USA, June 19, 2018, https://www.doctorswithoutborders.org/what-we-do/news-stories/news/msf-challenges-gileads-undeserved-patent-hepatitis-c-drug-china.
[279] Ed Silverman, “Gilead Patent for Its Hepatitis C Drug Is Invalidated by Chinese Authorities,” *STATNews*, August 13, 2018, https://www.statnews.com/pharmalot/2018/08/13/gilead-patents-hepatitis-china/.

The United States Trade Representative (USTR) is an agency within the US government, associated with the Executive Office of the President. Its job is to implement US trade policy. It also maintains the "annual priority watch list of countries", which are countries that it sees as needing to be pressured, one way or another, into acting to protect intellectual property, particularly that of American businesses. The attempted use of compulsory licenses (in line with TRIPS) by many countries has landed them on that list. A recent USTR report drew special attention to the attempts by MSF to obtain Hepatitis C medications as a threat to US intellectual property. From USTR's framing, it seems apparent that they are using TRIPS only where it suits American business, effectively bullying other countries out of invoking the parts of the treaty that are intended to ensure access to these inventions for public health purposes.

Another drawback to the production of generic medications is quality assurance. Organizations like WHO try to qualify generic producers as well as document which generic medications have been approved by appropriately stringent regulatory agencies. This ensures that the medications provided not only do what they should, but also that they won't actually cause harm to the people taking them. The process of WHO approval can take longer than a year and a half, but fake versions of these products have been identified in some countries. Falsified generic drugs are very difficult to detect without laboratory testing, a resource that not all practitioners can access.[280]

Another barrier to obtaining these drugs for low income countries is the registration process. Each country needs to approve the drugs that will be used and sold

[280] World Health Organization, “Global Report on Access to Hepatitis c Treatment: Focus on Overcoming Barriers.”

within its borders. Usually this process includes local clinical trials, though in some cases the requirement for them can be waived. Because of this process, companies like Gilead prioritize which countries to go through the registration process with first, delaying the approval of these drugs in countries where the potential market is smaller. It's also a barrier to use of generic drugs.[281]

The alternative to using TRIPS flexibilities is negotiating prices, but the barrier countries face here is transparency in drug pricing. In order to negotiate for a product, you need to have some information about what everyone else is paying and why in order to ensure you're getting a reasonable deal. WHO provides information about the prices each country pays, but also is pushing for further transparency.[282] Countries that have used negotiations to their advantage include the UK and Australia. The UK has managed to negotiate a deal with several companies, despite a court case by AbbVie, complaining about the fairness of the process to obtain wider access to the medications for the National Health Service.[283] Australia piloted the Netflix model, paying a lump sum to obtain access for all its patients.[284]

In 2017, MSF published *Hepatitis C: Not Even Close.* It cited high costs, regulatory barriers, and patents as some of the most substantial barriers to Hepatitis C treatment. Despite the heartening progress Egypt, Pakistan, and a handful of other countries have made, *Not Even Close* is a fair characterization of the situation regarding

[281] World Health Organization.
[282] World Health Organization, "Progress Report on Access to Hepatitis C Treatment: Focus on Overcoming Barriers in Low- and Middle-Income Countries."
[283] Ed Silverman, "U.K. Reaches 'first-of-Its-Kind' Deal with Drug Makers for Hepatitis C - STAT," *STAT News*, April 30, 2019, https://www.statnews.com/pharmalot/2019/04/30/uk-hepatitis-drug-prices/.
[284] World Health Organization, "Progress Report on Access to Hepatitis C Treatment: Focus on Overcoming Barriers in Low- and Middle-Income Countries."

Hepatitis C worldwide today.[285] The viral hepatitis epidemic continues to claim more lives yearly than those claimed by HIV/AIDS. Where Hepatitis C is concerned, progress remains halting and localized. One of the countries that has successfully mounted a response is Egypt.

[285] Medecins Sans Frontieres, "Hepatitis C - Not Even Close," Issue Brief, October 29, 2017, https://msfaccess.org/hepatitis-c-not-even-close.

CHAPTER 14

SUCCESS IN EGYPT

Hepatitis C had been a chronic health issue in Egypt since the mid- 20th century, when the country had eliminated one disease, shistosomiasis, but in the process spread Hepatitis C. But Egypt's response to Hepatitis C has been stunningly successful. About 40% of the patients around the world treated for Hepatitis C by 2016 were in Egypt, and the initiative's success has only increased since then. Egypt is a middle-income country, not covered by the voluntary licenses that make Hepatitis C treatment available to 100 low income countries. So how did it obtain the medications?

Egypt's original problem with Hepatitis C stems from another disease, schistosomiasis. Common in tropical regions of the world, schistosomiasis is caused by a trematode, a parasitic flatworm that spends part of its lifecycle in human tissues. Schistosomiasis is contracted by contact with contaminated water. The larval forms of the trematodes can burrow through human skin and enter the bloodstream where they reproduce and release eggs. These eggs are specially modified to make their way through tissues, ideally exiting through feces or urine, but some of them get stuck in the body. These locations can vary depending on what species of schistosome the host has. *Schistosoma haematobium*, the common species in Egypt, tends to get stuck in the liver and intestines.

A few of these lost parasites aren't a big deal. The body surrounds the larva with a calcified shell, and carries on with business as usual. But if a patient has a lot of these little larvae in their tissues, this calcification becomes an issue in and of itself, compromising and scarring organs. When a liver is severely affected, this is called *clay*

pipe stem fibrosis, because the calcification becomes so severe that the affected organ has areas that look and feel like clay.[286] Schistosomiasis was a major health problem for Egypt, and a major cause of liver disease.

In the 1950s, the Egyptian government launched a campaign to eliminate shistosomiasis. The treatment available was a series of injections of tartar emetic, which is an arsenical compound that's very effective but toxic.[287] Treatment involved as many as twelve doses of this drug, at a time when using syringes multiple times on multiple people was the norm, and as a result, spread bloodborne diseases. Egypt would have to wait until the 1980s before getting access to a schistosomiasis treatment in pill form.[288]

Hepatitis C is, as we know, asymptomatic for many patients until it starts to damage the liver, so at first, the schistosomiasis campaign seemed like a success—infections with all the Schistosoma species had decreased. But there were still cases of liver disease. By the 1990s, Egypt realized it had a serious problem.[289] A few years before the approval of sofosbuvir, it led the world in Hepatitis C infections, with over 14% of its population testing positive.[290] Not only had the disease spread through the initial schistosomiasis campaign, it had then continued to be transmitted through blood products and through its other common routes: exposure to at-home procedures involving

---

[286] José de Souza Andrade-Filho, "LETTER TO THE EDITOR ANALOGIES IN MEDICINE: WHITE CLAY-PIPE STEM 'CIRRHOSIS,'" *Revista Do Instituto de Medicina Tropical de São Paulo* 56, no. 1 (2014): 92, https://doi.org/10.1590/S0036-46652014000100016.
[287] Satyavan Sharma and Nitya Anand, "Chapter 4 - Organometaliics," in *Pharmacochemistry Library*, ed. Satyavan Sharma and Nitya Anand, vol. 25, Approaches to Design and Synthesis of Antiparasitic Drugs (Elsevier, 1997), 124–47, https://doi.org/10.1016/S0165-7208(97)80026-8.
[288] Strickland, "Liver Disease in Egypt."
[289] M. Farid Abdel-Wahab et al., "High Seroprevalence of Hepatitis C Infection among Risk Groups in Egypt," *The American Journal of Tropical Medicine and Hygiene* 51, no. 5 (November 1, 1994): 563–67, https://doi.org/10.4269/ajtmh.1994.51.563.
[290] F. DeWolfe Miller and Laith J. Abu-Raddad, "Evidence of Intense Ongoing Endemic Transmission of Hepatitis C Virus in Egypt," *Proceedings of the National Academy of Sciences* 107, no. 33 (August 17, 2010): 14757–62, https://doi.org/10.1073/pnas.1008877107.

injections, transmission from mother to child, between partners, or use of shared razors all being potential paths of infection.[291]

The initial price of sofosbuvir was daunting. A drug that arrived on the US market at $84,000 USD/course of treatment was well out of reach. To treat every affected patient would have cost trillions of dollars, multiple times the country's GDP. If Egypt wanted to solve its Hepatitis C problem, first it was going to have to get creative in its negotiations.

Fortunately, it had two things in its favor: a lot of potential patients, and it hadn't yet issued a patent for the drug. It successfully negotiated the cost down to $900 per patient, a deal several other countries managed to reach with Gilead. Still, it was pricey, and Egypt had a lot of patients to treat. It ended up not granting the patent, and generic production of the drug got them a price under $100, very close to the price of production.[292]

But obtaining a drug and getting it to the people who need it are two different challenges. You need to have people willing to be screened for the disease, which is difficult if that disease is associated with stigmatized activities or groups. This was the case in Egypt as it is in the United States. Then you need to make sure that the people who are diagnosed with the disease access treatment and then complete it. To accomplish these steps, the Egyptian Ministry of Health worked with the World Health Organization to first find out what people thought about the disease. How was it transmitted? What were the common misunderstandings? What are people doing to avoid it? Would average

[291] Mostafa K. Mohamed et al., "Intrafamilial Transmission of Hepatitis C in Egypt," *Hepatology* 42, no. 3 (September 1, 2005): 683–87, https://doi.org/10.1002/hep.20811.
[292] Ted Alcorn, "Why Egypt Is at the Forefront of Hepatitis C Treatment," The Atlantic, May 29, 2018, https://www.theatlantic.com/health/archive/2018/05/why-egypt-is-at-the-forefront-of-hepatitis-c-treatment/561305/.

citizens want to take advantage of a screening and treatment program? What stigmas had to be overcome? Then the government had to craft a media campaign to address common misunderstandings.[293]

Between 2015-2017, more than a million people were treated for Hepatitis C, the prevalence had fallen to 6.3% of the population rather than 14.7%, and the government aimed to reach 42 -53 million people by April 2019, almost the entire adult population.[294] An incentive for getting tested was associated screening for diabetes and high blood pressure.[295]

Despite this success, challenges remain. One of these challenges is reaching the individuals who haven't been tested yet, estimated in early 2019 as 3-4 million more people. Transmission continues in the country, with an estimated 150,000 new infections yearly.[296] Blood product screening is still not at an effective level, enabling transmission through the blood supply.[297] An Egyptian Ministry of Health official speaking at HepDart , the hepatology meeting I attended in December 2019, cited shorter courses of treatment as a need, in the hopes they would increase treatment adherence.[298]

---

[293] World Health Organization, "WHO EMRO | Egypt Launches National Communication Campaign on Hepatitis C | Egypt-Events | Egypt," accessed February 3, 2020, http://www.emro.who.int/egy/egypt-events/hepatitis-c-campaign.html.
[294] Miller and Abu-Raddad, "Evidence of Intense Ongoing Endemic Transmission of Hepatitis C Virus in Egypt"; World Health Organization, "WHO | Egypt: 35 Million People Receive Hepatitis C Test," WHO, March 30, 2019, http://www.who.int/hepatitis/news-events/egypt-hepatitis-c-testing/en/.
[295] Mahmoud Mourad and Lena Masri, "Millions Flock to Free Tests as Egypt Seeks to Eradicate Hepatitis C - Reuters," accessed February 3, 2020, https://www.reuters.com/article/us-health-egypt-hepatitis-c/millions-flock-to-free-tests-as-egypt-seeks-to-eradicate-hepatitis-c-idUSKBN1O21IO.
[296] World Health Organization, "WHO | Egypt."
[297] Mahmoud Mourad and Lena Masri, "Millions Flock to Free Tests as Egypt Seeks to Eradicate Hepatitis C," *Reuters*, December 3, 2018, https://www.reuters.com/article/us-health-egypt-hepatitis-c-idUSKBN1O21IO.
[298] Manal El-Sayed, "Elimination of HCV in Egypt: A Global Model," in *Confrence Proceedings from HepDART 2019*, vol. 1 (HepDart, Tucker, GA: Global Hepatitis Journal, 2019), https://informedhorizonseducation.com/scientific-program?utm_term=0_73d2edd14c-8126873a32-66369597.

But of the challenges that Egypt faces, affording the medications needed to treat the disease is not one. Through both a negotiation with the manufacturer, and then the use of generic drugs, Egypt has managed to procure the direct acting antivirals it needs to stem the tide of one of the biggest Hepatitis C epidemics in the world. Egypt's Ministry of Health marketed the need to get tested, and then made barriers to treatment as low as possible, while ramping up screenings. This is the sort of initiative that's vital to deal with a disease that doesn't show symptoms for many years. That marketing also involved a concentrated effort to decrease the stigma associated with Hepatitis C, to encourage more people to come forward to be screened and treated. Testing was made as convenient to access as possible, the media campaign encouraged people to access it and other health services at the same time, and as a result, peer pressure to get tested also came to bear. It's an important lesson for other countries facing their own Hepatitis C epidemics. With sufficient political will and government engagement, a lot of progress can be made, even in countries without significant resources.[299]

In the United States, however, barriers to treatment access are extremely high, with government agencies playing actively obstructionist roles, motivated by the cost of treating the patients in their care. Stigma surrounding the disease is likewise high. Older individuals are more likely to have contracted the disease through healthcare procedures, but this is a relatively new message. Patients speak of the dreaded question, "How did you get this?"[300] and the judgement that ensues, since Hepatitis C is so strongly associated with opioid use. While the opioid epidemic *is* driving the spread of the disease

[299] World Health Organization, “WHO | Egypt.”
[300] Anonymous Provider or Patient Interview.

in younger subpopulations, that stigma is actively impeding its containment, as are the government policies aimed at excluding people who inject drugs from treatment access. This in turn discourages people from getting tested in the first place, because of the fear of that stigma, and also because they doubt they'll be able to access treatment anyway. In short, for every technique that Egypt's campaign against Hepatitis C has demonstrated to be effective, the United States is doing the opposite. The US is currently included in WHO's list of the top ten countries contributing to the global burden of Hepatitis C.[301] If we ever wish to move off that list, we will have to make major changes in our strategy.

Gilead's pricing decisions for its Hepatitis C drugs created many problems in the public health realm. In the last chapters, we've seen how systems, both within the United States and internationally, struggled to absorb these costs, and how some countries, Egypt in particular, devised strategies to avoid implementing barriers to treatment and lower Hepatitis C infections. But Gilead's pricing decisions didn't just negatively affect public health. They also had an impact on Gilead's bottom line.

[301] World Health Organization, "Progress Report on Access to Hepatitis C Treatment: Focus on Overcoming Barriers in Low- and Middle-Income Countries."

CHAPTER 15

GILEAD'S WOES

For the first two years sofosbuvir and Harvoni were on the market, Gilead did amazingly well, making $12.5 billion from its Hepatitis C drugs in 2015 alone.[302] But the company hasn't seen another year as successful as 2015. Despite holding a patent on sofosbuvir, a drug that's the backbone of many of the curative therapies for the 71 million patients around the world, a combination of a declining market share and rising competition caused Gilead's profits to fall steadily. By mid-2019, Hepatitis C-related sales only reached $842 million. The company has cited increased competition, decreased prices, and a declining patient pool as reasons behind this decline in profits.[303] As earlier noted, the idea that the Hepatitis C patient pool was shrinking flew in the face of epidemiological data.[304] Gilead's woes haven't been limited to the Hepatitis C realm. Its research and development efforts, particularly in noninfectious liver disease, haven't been fruitful.[305] In 2016, Gilead's CEO, John Martin, stepped down to become the executive chairman. Martin and his replacement, John Milligan, left the company in 2018.[306] The

---

[302] Tae Kim, "Goldman Sachs Asks in Biotech Research Report: 'Is Curing Patients a Sustainable Business Model?,'" *CNBC*, April 11, 2018, https://www.cnbc.com/2018/04/11/goldman-asks-is-curing-patients-a-sustainable-business-model.html.

[303] "Gilead Sciences Announces Second Quarter 2019 Financial Results," July 30, 2019, https://www.gilead.com/news-and-press/press-room/press-releases/2019/7/gilead-sciences-announces-second-quarter-2019-financial-results.

[304] CDC National Center for Injury Prevention and Control, "2019 Annual Surveillance Report of Drug-Related Risks and Outcomes."

[305] Amirah Al Idrus, "'Another Swing, Another Miss' for Gilead as NASH Combo Flops in Phase 2," *FierceBiotech*, December 16, 2019, https://www.fiercebiotech.com/biotech/another-swing-another-miss-for-gilead-as-nash-combo-flops-phase-2; "Gilead Combination Therapy for NASH Misses Primary Phase II Trial Goal," *Clinical Trials Arena* (blog), December 17, 2019, https://www.clinicaltrialsarena.com/news/gilead-nash-trial-atlas-fails/.

[306] Jen Weiczner, "Gilead CEO John Martin Is Stepping Down After 20 Years," *Fortune*, accessed February 4, 2020, https://fortune.com/2016/01/29/gilead-ceo-john-martin/; Kristen Brown, "Gilead's Top Management Is Leaving at End of an Era for Biotech," *Bloomberg*, July 25, 2018,

company is now facing a lawsuit unrelated to its Hepatitis C treatments from the Department of Health and Human Services, citing its unwillingness to reach an agreement with HHS to obtain HIV preventative treatments that relied on federally funded research.[307] Criticism of the company's practices has continued, both in the United States and internationally.

The congressional investigation in 2015 prompted a slew of negative press about Gilead, painting a picture of a company far more interested in maximizing profit than treating patients. In the public eye it was not a flattering conclusion, even if Gilead's strategy had not, in fact, maximized its profits.

At the same time, other companies entered the market AbbVie launched its own direct acting antivirals in 2016.[308] State Medicaid programs were quick to arrange with AbbVie to obtain the medications at far lower prices than Gilead's.[309] Merck was quick to follow.

In response, Gilead lowered prices and marketed Epclusa, a new direct acting antiviral that was broadly effective across all Hepatitis C genotypes.[310] Then Gilead launched its own generics for Epclusa and Harvoni. Both were priced at $24,000 per

---

https://www.bloomberg.com/news/articles/2018-07-26/gilead-s-top-management-is-leaving-at-end-of-an-era-for-biotech.

[307] Ed Silverman, "HHS Sues Gilead for Refusing to Do Licensing Deal on HIV Prevention Pills," *STAT*, November 7, 2019, https://www.statnews.com/pharmalot/2019/11/07/hhs-gilead-hiv-prevention-patents-lawsuit/.

[308] "AbbVie Receives U.S. FDA Approval of Once-Daily VIEKIRA XR™ (Dasabuvir, Ombitasvir, Paritaprevir and Ritonavir) for the Treatment of Genotype 1 Chronic Hepatitis C | AbbVie News Center," July 25, 2016, https://news.abbvie.com/news/abbvie-receives-us-fda-approval-once-daily-viekira-xr-dasabuvir-ombitasvir-paritaprevir-and-ritonavir-for-treatment-genotype-1-chronic-hepatitis-c.htm.

[309] Aleccia, Ostrov, and Blankinship, "As AbbVie Fights Hepatitis C, States Make Secret Deals with Drugmakers."

[310] Michael Douglass, "Has Gilead Sciences' Cash Cow Finally Hit Bottom?," *The Motley Fool* (blog), January 23, 2017, https://www.fool.com/investing/2017/01/23/has-gilead-sciences-cash-cow-finally-hit-bottom.aspx.

course of therapy in 2018.[311] Yet still, profits declined, with analysts noting that Gilead was attempting a balancing act between treating more people for less money, or fewer people for more.[312] This decline in profits implies that Gilead's high pricing of its Hepatitis C drugs had, by locking potential paitents out of the customer pool, actually squandered the advantage it had enjoyed as the first company to bring a product to market. It instead had created a pool of untreated patients who turned to its competitors.

A Goldman Sachs research report in early 2018 claimed that curing patients wasn't a lucrative business model, citing Gilead's decline in profits as a case in point.[313] This report did not take into account the actual number of patients still suffering from Hepatitis C. Before sofosbuvir's approval, high estimates put the US Hepatitis C population at about 3.4 million, current estimates are still hovering around 2.4 million.[314] The patient pool had not in fact declined in the way Goldman Sachs assumed it had. More than two thirds of patients hadn't been treated at all—one can only suppose that the report was based solely off of Gilead's revenues without taking into account the epidemiological reality. Among the most vulnerable populations, like the people I interviewed at the harm reduction program in Phoenix, the need for treatments remains extremely high. Treatment of prisoners remains low, and lawsuits to gain access for prisoners are ongoing in multiple states.

---

[311] Gilead Sciences, "Gilead Subsidiary to Launch Authorized Generics of Epclusa® (Sofosbuvir/Velpatasvir) and Harvoni® (Ledipasvir/Sofosbuvir) for the Treatment of Chronic Hepatitis C," accessed October 15, 2019, https://www.gilead.com/news-and-press/press-room/press-releases/2018/9/gilead-subsidiary-to-launch-authorized-generics-of-epclusa-sofosbuvirvelpatasvir-and-harvoni-ledipasvirsofosbuvir-for-the-treatment-of-chronic.
[312] Douglass, "Has Gilead Sciences' Cash Cow Finally Hit Bottom?"
[313] Tae Kim, "Goldman Asks: 'Is Curing Patients a Sustainable Business Model?,'" *CNBC*, April 11, 2018, https://www.cnbc.com/2018/04/11/goldman-asks-is-curing-patients-a-sustainable-business-model.html.
[314] Aleccia, Ostrov, and Blankinship, "As AbbVie Fights Hepatitis C, States Make Secret Deals with Drugmakers."

So how can Gilead be suffering from a reduced patient pool at the same time that so many patients cannot access treatment? There are two populations most affected by Hepatitis C: older patients who contracted the disease through healthcare procedures, and younger patients who contracted the disease through injection drug use. Older patients have been prioritized; the latter group has to overcome extensive and in cases, illegal barriers to access treatment, such as sobriety and severity-of-disease restrictions. Because many older patients have been treated does not mean the others have ceased to exist. The market for Gilead's treatments still exists, but Gilead's pricing practices spurred the creation of bureaucratic structures by payers that actively excluded some of the riskiest patients. These structures are directly attributable to Gilead's initial pricing decisions, but as prices have dropped the treatment restrictions have remained.

The declining patient pool has less to do with efficacious drugs being unprofitable and more to do with drug pricing and health systems making treatment difficult to access. But the perception of declining patient populations made stock analysts jumpy anyway. One writer for The Motley Fool claimed that Hepatitis C profits could "[go] fully to zero" because of that shrinking customer base. [315] The Goldman Sachs report cited Gilead as a reason that effective drugs could backfire by curing your customer base, even if the majority of that customer base hadn't actually been cured.[316] At the end of the day, because they hadn't considered the epidemiological realities of the disease, analysts walked away with the wrong lesson. The real lesson was that, by pricing sofosbuvir so highly, Gilead had closed most of its customer base out of the market, limiting its own

[315] Michael Douglass, "I Was Wrong About Gilead Sciences -," *The Motley Fool* (blog), March 9, 2017, https://www.fool.com/investing/2017/03/09/i-was-wrong-about-gilead-sciences.aspx.
[316] Kim, "Goldman Sachs Asks in Biotech Research Report."

profits and managing to record a decline in revenue even as millions of Hepatitis C patients went untreated.

And not only untreated, because untreated patients can transmit the disease. Indeed, because of the cryptic nature of Hepatitis C infection, without universal testing, there's every likelihood that continuing transmission of Hepatitis C will keep the patient pool large and active for the foreseeable future. The new challenges Egypt is facing in testing its population and curtailing continuing transmission vividly illustrate that simply treating a disease isn't enough to stop an epidemic. The idea that curing patients is a threat to the business future of Hepatitis C treatment is claiming that the drugs have failed to continue delivering profits because they've been *too* successful.[317] In reality, it's hard to describe their public health impact as a success if the majority of Hepatitis C patients in the US are untreated.

Despite the declining revenues from its Hepatitis C drugs, Gilead was still attracting significant criticism for its high prices, along with its other business practices. In July 2016, the group Americans for Tax Fairness published a report showing that Gilead had offshored its patents to avoid income taxes in the United States, spending the majority of its revenue on share buybacks, and on having used millions in taxpayer dollars to develop the Hepatitis C drugs it then priced so highly. [318] Support for this is unclear, as my own research seemed to indicate that most NIH funding was for unrelated compounds. See Appendix 1.

[317] Kim.
[318] "Gilead Sciences: Price Gouger, Tax Dodger," *Americans For Tax Fairness* (blog), July 13, 2016, https://americansfortaxfairness.org/new-report-gilead-sciences-price-gouger-tax-dodger/.

The offshoring meant that the company's Irish subsidiary received ownership of the patents, which then couldn't be taxed the same way they would have been in the United States. The catch in this, for Gilead, was that those profits couldn't be brought back to the US. They were stuck in Ireland unless the tax code changed. The Irish subsidiary is doing well, in contrast to the challenges its American parent faces.[319] In 2019, the passing of the 2017 tax law provided Gilead with an opportunity to transfer its intellectual property again, netting it $1.2 billion dollars of tax benefits. It then used $1.7 billion on stock purchases.[320]

With the Hepatitis C market declining, Gilead's attention turned to other diseases. A deal with a biotech company called Galapagos yielded a promising drug for inflammatory immune conditions, but in other cases, Gilead has not been as successful.[321] One of these diseases was Non-Alcoholic Fatty Liver Disease and, specifically, Non-Alcoholic Steatohepatitis, a major focus of the liver disease conference I attended in December of 2019. Shortly after the conference, several of Gilead's noninfectious liver disease drugs, one in Phase II clinical trials and another in Phase III, failed to treat the disease.[322]

---

[319] Gordon Deegan, "Profits Soar at Irish Arm of Gilead Even as Revenues Decline," *The Irish Times*, December 5, 2019, https://www.irishtimes.com/business/health-pharma/profits-soar-at-irish-arm-of-gilead-even-as-revenues-decline-1.4106163.
[320] Richard Rubin, "Companies Save Billions in Taxes by Shifting Assets Around Globe," *Wall Street Journal*, April 8, 2020, sec. US, https://www.wsj.com/articles/companies-save-billions-in-taxes-by-shifting-assets-around-globe-11586347201; "Gilead Sciences Announces Fourth Quarter and Full Year 2019 Financial Results," accessed October 7, 2020, https://www.gilead.com/news-and-press/press-room/press-releases/2020/2/gilead-sciences-announces-fourth-quarter-and-full-year-2019-financial-results.
[321] Michael McCoy, "Gilead and Galapagos Strike Big R&D Deal," *Chemical & Engineering News*, July 15, 2019, https://cen.acs.org/business/mergers-&-acquisitions/Gilead-Galapagos-strike-big-RD/97/web/2019/07.
[322] "Gilead Combination Therapy for NASH Misses Primary Phase II Trial Goal"; Al Idrus, "'Another Swing, Another Miss' for Gilead as NASH Combo Flops in Phase 2."

Gilead is now facing a lawsuit from the US Department of Health and Human Services. It alleges that one of Gilead's HIV drugs infringes on federal patents. Gilead's HIV drugs are one of its steadiest sources of profit.[323] The lawsuit came after the company did not reach a licensing agreement with the federal government and is an unusual twist to the usual behavior of the US federal government in regard to its patents. The basic research that allowed the development of the two drugs, Truvada and Descovy, was funded by the CDC, which holds patents. These two drugs form a regime known as PrEP, which prevents people exposed to HIV from contracting the disease. The lawsuit was filed in November of 2019. Its outcome is still pending.[324]

Still beleaguered by its 2019 failures in clinical trials, Gilead has set its hopes upon remdesivir, another direct acting antiviral. Remdesivir was originally developed to treat Ebola Virus Disease, but failed to produce results. Now, the drug seems to have some effect on COVID-19, though not nearly as strong a one as sofosbuvir does on Hepatitis C. When remdesivir first showed promise, Gilead Sciences attempted to file to get it orphan drug status, citing the low number of infections in the US to establish the disease's rarity and justify the move. In order to qualify, the disease must affect fewer than 200,000 people within the United States. COVID-19 had only caused about 50,000 infections in March 2019 when Gilead applied, and received, orphan drug status.[325]

---

[323] Jeremy C. Owens, "Gilead Earnings Show Surprising Sales Increase amid Massive Change," MarketWatch, accessed February 4, 2020, https://www.marketwatch.com/story/gilead-earnings-show-surprising-sales-increase-amid-massive-change-2019-07-30.
[324] "United States v. Gilead Sciences, Inc.," *Patent Docs* (blog), accessed February 4, 2020, https://www.patentdocs.org/2019/12/united-states-v-gilead-sciences-inc.html; Silverman, "HHS Sues Gilead for Refusing to Do Licensing Deal on HIV Prevention Pills."
[325] Sydney Lupkin, "FDA Grants Experimental Coronavirus Drug Benefits For Rare Disease Treatments," *NPR.Org*, March 24, 2020, https://www.npr.org/sections/health-shots/2020/03/24/821035311/fda-grants-experimental-coronavirus-drug-benefits-for-rare-disease-treatments.

Orphan drug status confers certain benefits upon the drugs that merit it, including a seven-year monopoly that prevents the creation of generic versions of the drug, tax credits, and the waiving of FDA fees.[326] Public outcry prompted Gilead to withdraw the application, and it has now donated 940,000 doses to hospitals.[327] This act of charity is somewhat balanced by Gilead's decision to price the drug at $3,120 for a five day course of treatment, a price that has drawn criticism given the drug is of limited efficacy in the sickest patients.[328] That price works out to $520 per vial.[329] According to some projections, remdesivir stands to make an estimated $9 billion in its first two years.[330]

Even with lowered prices, many states, including Arizona, still have the restrictive policies that make access to Hepatitis C treatment difficult to access for some of the patients most in need. The original reasons for these policies was price, and price probably still plays a role in their continuation. Gilead may have a problem with a declining patient pool, but it's one of their own initiation. Sofosbuvir's pricing didn't just cause it to fall short of its public health potential, but also of its business potential as well. Gilead had miscalculated the benefits of price versus volumes: it had opted to price the drug highly, restricting the volume of potential sales. As its declining profits show, this did not pay off. In the end, the pricing strategy Gilead pursued seems was unsustainable,

---

[326] Lupkin; Manas Mishra and Michael Erman, "Gilead Asks FDA to Take Back Lucrative Orphan Drug Status on Possible Coronavirus Treatment," *Reuters*, March 25, 2020, https://www.reuters.com/article/us-health-coronavirus-gilead-sciences-idUSKBN21C3MG.
[327] Eric Boodman, "Gilead Ups Its Donation of the Covid-19 Drug Remdesivir," *STAT*, May 19, 2020, sec. Exclusive, https://www.statnews.com/2020/05/18/coronavirus-gilead-ups-remdesivir-donation/.
[328] William A. Haseltine, "The Other Shoe Drops: Gilead's Outrageous Pricing Of Remdesivir," *Forbes*, June 29, 2020, sec. Innovation, https://www.forbes.com/sites/williamhaseltine/2020/06/29/the-other-shoe-drops-gileads-outrageous-pricing-of-remdesivir/; Lupkin, "Remdesivir Priced At More Than $3,100 For A Course Of Treatment."
[329] Lupkin, "Remdesivir Priced At More Than $3,100 For A Course Of Treatment."
[330] Christopher Rowland, "Remdesivir May Not Cure Coronavirus, but It's on Track to Make Billions for Gilead," *Washington Post*, October 30, 2020, https://www.washingtonpost.com/business/2020/09/30/remdesivir-drug-coronavirus-gilead/.

and set in motion systems that strictly limited that patient pool, excluding the populations where transmission is arguably highest. While not the only factor in their declining Hepatitis C profits, it has been a major one, and it has worsened over a period when they have had major setbacks in their research and development of new drugs. In short, Gilead's pricing strategy didn't just hurt Hepatitis C patients, it hurt Gilead's long-term business as well.

While Gilead suffered the fallout of its pricing scheme, frustrated patients and activists were organizing to increase access to sofosbuvir.

CHAPTER 16

NOT GOING QUIETLY--ACTIVISM, HEPATITIS C, AND LEGISLATION

The health systems of the United States failed thousands of Hepatitis C patients, and they, and the activist organizations who represented them, have had enough.

Access to direct acting antivirals for prisoners was a point of contention throughout the drugs' short history. Few prisoners were able to obtain treatment, and prison systems, in many cases, no longer provided the older interferon treatments. Given that the price of treatment far outstripped many state prison systems' entire budgets, most prison systems had simply compensated by limiting treatment to a few. It kept the prison budgets in the black, but the price was measured in human lives and continued transmission.

Nowhere was this truer than in Missouri. Missouri had phased out the interferon treatments, and on paper, was providing DAA treatments based on patient health. In reality, few patients were getting treated, and some were dying while on the waitlist. Indeed, treatment access was getting worse, not better. Even if inmates managed to buy the drug themselves, the Department of Corrections barred them from receiving it.[331]

Because of this, the American Civil Liberties Union and the MacArthur Justice Center helped inmates launch a lawsuit in 2016, suing for better access to the drugs and to open the state to a class action lawsuit by all Hepatitis C positive inmates. The initial

[331] Alex Smith, “Locked Up And Untreated: One Missouri Inmate’s Quest For Hepatitis C Treatment,” May 9, 2018, https://news.stlpublicradio.org/post/locked-and-untreated-one-missouri-inmate-s-quest-hepatitis-c-treatment.

findings were in favor of the inmates, and were upheld in 2018 by an appeals court.[332] Missouri wasn't the only state facing these lawsuits. Texas inmates filed a lawsuit in 2019, calling lack of treatment cruel and unusual punishment and therefore unconstitutional under the Eighth Amendment.[333] A number of other states have also been sued, making state lawmakers nervous and interested in finding ways to treat their Hepatitis C positive prison populations.[334]

Outside of prison, the undertreated population consists of people who inject drugs. They've also been organizing. Their central argument is that denying treatment based on the use of illicit substances is essentially denying treatment based on a disability, and that the uneven access is an infringement on the constitutional rights of patients with substance abuse disorder. At least one state is facing organized pushback from these groups. It is likely more will follow.

The Centers for Medicare and Medicaid Services, the federal body that oversees state Medicaid activities, is unlikely to offer support to state Medicaid programs that face these challenges. They've already made their position clear via a 2015 letter, which points out that, under the Social Security Act, state Medicaid programs that have opted to cover prescriptions cannot deny beneficiaries medications appropriate for their illness. The

---

[332] Sarah Fentem, "Appeals Court Upholds Class Action Status for Thousands of Missouri Inmates with Hepatitis," December 6, 2018, https://news.stlpublicradio.org/post/appeals-court-upholds-class-action-status-thousands-missouri-inmates-hepatitis.
[333] Keri Blakinger, "Texas Inmates Sue for Hepatitis C Drug, Alleging Lack of Treatment Is 'Cruel and Unusual,'" *Huston Chronicle*, September 18, 2019, https://www.houstonchronicle.com/news/houston-texas/houston/article/Texas-inmates-sue-for-hepatitis-C-drug-alleging-14453099.php.
[334] Jonathan Shorman, "591 Kansas Inmates Have Hepatitis C. It Would Cost about $9 Million to Treat Them All," *Kansas City Star*, February 20, 2019, https://www.kansascity.com/news/politics-government/article226528715.html.

letter has been toothless, and many state Medicaid programs, including Arizona's, have ignored it, but it may prove useful should the issue go to court.

I tried to contact Arizona's state Medicaid program, the Arizona Health Care Cost Containment System, to ask for further information on the state's reluctance to provide direct acting antivirals to the patients for whom it is responsible. Despite the decline in prices of direct acting antivirals, there has been little revision of the requirements. My questions went unanswered. We will have to wait for the (likely inevitable) court case to learn more about AHCCCS's motivations in restricting access to Hepatitis C treatments.

But the story of poor treatment access isn't just a story of Hepatitis C. It's a nearly universal problem within the American healthcare system. In 2015 and 2016, price hikes for HIV drugs, EpiPens, and insulin scandalized the country. Details for each of these cases were different from the case of sofosbuvir, which was a new drug. All the drugs in these cases were long out of patent, but their manufacturers had elected to vastly inflate their prices.

Despite the outrage they provoked, prices haven't returned to their original levels. Indeed, it took the emergency of COVID-19 before insulin manufacturers granted any kind of price relief to their patients, many of whom depend on a specific form of the drug.

Despite decrying astronomical drug prices during the 2016 election, the Trump Administration so far has done very little to decrease the pricing crisis that now faces the US. Indeed, during COVID-19, the administration has frequently capitulated to pharmaceutical companies and medical device manufacturers alike. The Trump

Administration has indicated its sympathy with Gilead's pricing decisions for remdesivir, despite its limited efficacy.

As it buckles to Gilead, the administration has also caved to device manufacturers. Lingering alarm over the anthrax scare prompted the Bush Administration to create BARDA (Biomedical Advanced Research and Development Agency) to address national security risks related to biological, radiological, chemical, and nuclear attacks, as well as to address the threat of infectious diseases. One particular source of concern was the lack of ventilators. Ventilators provide mechanical assistance in breathing to patients too ill to do so themselves. They're most useful for treating severe pneumonias, which can be caused by influenza viruses, and, notably, COVID-19. Back in the early 2000s, the primary pandemic bugbear was a pandemic flu, and in order to better prepare the United States for this, BARDA offered a grant to companies willing to develop a ventilator that was easy to operate (most aren't), could be stored for long periods of time (most can't), could be operated with a minimum of training (most are complex) and would be streamlined enough to be easily transported (most are bulky).[335] A company took the contract in 2008, skipped out of it in 2010, and a second company picked it up in 2014. That company, Phillips Resperonics, only received FDA approval for its new ventilator, the Trinity EVO ventilator, in September of 2019. None had been produced when

[335] Robert L. Chatburn and Eduardo Mireles-Cabodevila, "Chapter 3. Basic Principles of Ventilator Design," in *Principles and Practice of Mechanical Ventilation*, ed. Martin J. Tobin, 3rd ed. (New York, NY: The McGraw-Hill Companies, 2013), accessmedicine.mhmedical.com/content.aspx?aid=57061171; Nicholas Kulish, Sarah Kliff, and Jessica Silver-Greenberg, "The U.S. Tried to Build a New Fleet of Ventilators. The Mission Failed.," *The New York Times*, March 29, 2020, sec. Business, https://www.nytimes.com/2020/03/29/business/coronavirus-us-ventilator-shortage.html; Sebastian Rotella and Patricia Callahan, "Taxpayers Paid Millions to Design a Low-Cost Ventilator for a Pandemic. Instead, the Company Is Selling Versions of It Overseas.," *ProPublica*, March 30, 2020, https://www.propublica.org/, https://www.propublica.org/article/taxpayers-paid-millions-to-design-a-low-cost-ventilator-for-a-pandemic-instead-the-company-is-selling-versions-of-it-overseas-.

COVID-19 arrived in the US. None had been given to the US government in April of that year, as the specter of a surge in cases prompted hospitals to draw up ventilator triage plans, deciding who would live and who would die should the number of patients in need exceed the number of available ventilators. But the ventilators had indeed been made; Phillips was doing a brisk trade with private entities, and was selling ventilators for prices between $12,459 and $17,154, with significant backorders.[336]

The Trump Administration was reluctant to stop these private sales, and indicated that it had no intentions to pressure Phillips to produce the ventilators before the Fall 2021 deadline in its contract, despite the deadly pandemic. Phillips indicated that it was uninterested in doing anything but fulfilling the letter of its contract.[337] Eventually, a deal negotiated by the administration allowed Phillips to provide a different ventilator, the E1, to the government at a much higher cost—roughly $15,000 per ventilator.[338] Phillips claimed the ventilator was more suited to the needs of COVID-19 patients. However, the ventilator was not in fact FDA approved, and was only permitted on an emergency use basis.[339] Instead of standing up to pharma companies, as the campaign had promised, the Trump Administration had given a misbehaving company $646.7 million taxpayer dollars into the question.[340]

---

[336] Kulish, Kliff, and Silver-Greenberg, "The U.S. Tried to Build a New Fleet of Ventilators. The Mission Failed."; Rotella and Callahan, "Taxpayers Paid Millions to Design a Low-Cost Ventilator for a Pandemic. Instead, the Company Is Selling Versions of It Overseas."
[337] Kulish, Kliff, and Silver-Greenberg, "The U.S. Tried to Build a New Fleet of Ventilators. The Mission Failed."
[338] David Shepardson, "GM, Philips to Supply 73,000 U.S. Ventilators in $1.1 Billion Effort," *Reuters*, April 8, 2020, https://www.reuters.com/article/us-health-coronavirus-gm-idUSKBN21Q1YA.
[339] "Philips Introduces New Philips Respironics E30 Ventilator to Help Free up ICU Units in Wake of COVID-19," Philips, April 14, 2020, https://www.philips.com/a-w/about/news/archive/standard/news/articles/2020/20200414-philips-introduces-new-philips-respironics-e30-ventilator-to-help-free-up-icu-units-in-wake-of-covid-19.html.
[340] Shepardson, "GM, Philips to Supply 73,000 U.S. Ventilators in $1.1 Billion Effort."

The Trinity EVO ventilator story mirrors the major problem in the Hepatitis C story; a company conducting its business within the letter of the law can currently get away with putting millions of lives in jeopardy in the name of profit. The effective defanging of laws like Bayh-Dole and the extreme reluctance to use §1498 are political decisions that have effectively taken the brakes off of a runaway system. Bayh-Dole should have been a reasonable way to jumpstart American innovation, and it would have been the control on the system that march-in represented ever been allowed to be functional. As it is, the law has become what its original detractors feared—the concession of a hugely unmitigated advantage to patentholders at the expense of the American taxpayers who initially funded their research.

Each of these cases also illuminates possibilities for adjusting these systems for better outcomes. They are examples of the way in which our current systems impede access to treatment, but also highlight our existing policy tools for intervention. The story of sofosbuvir is an informative one, because of the number of opportunities for intervention, and how thoroughly the failure to use these opportunities affected all parties involved, including Gilead Sciences itself.

CHAPTER 17

WHAT WE CAN DO

The story of sofosbuvir is all the more frustrating because its failures were avoidable. It wasn't that the United States lacked the wherewithal to respond to the crisis the pricing of sofosbuvir caused. It was that, time after time, the laws that should have acted as brakes on the runaway train of pricing were not activated. In some ways, we may simply not know the extent of the system failure of which sofosbuvir's pricing was symptomatic because the details of drug prices and federal funding are so opaque.

Checks and balances are only significant if the political will to use them is present. That political will, despite a full third of Americans not taking prescription drugs as advised by their doctors because of price, remains nonexistent, or at the very least, not acted upon.[341] Let's summarize how that lack of political will, combined with the policies in question, and the substantial profit motive of Pharmasset and Gilead, combined to give us sofosbuvir, a drug that's never gotten its chance.

Hepatitis C is a deadly disease that inflicts incredible misery upon its victims. Until 2013, the only treatment was interferon, which was a misery to endure and failed to treat 70% of its recipients. A small pharmaceutical startup, founded by a Veterans Affairs researcher using his personal research allowance ($1/8^{th}$ of his work week) recruited a brilliant group of scientists and grant money to cure it. The only federal grant money that touched the drug was a $244,470.25 grant from the IRS under the Qualifying Therapeutic

[341] Lopes, Wu, and 2019, “KFF Health Tracking Poll – February 2019.”

Discovery Program.[342] Some of the testing of the precursors to sofosbuvir was conducted in academic laboratories funded by NIH funding.[343]

Amazed and encouraged by the drug's success, Gilead Sciences purchased Pharmasset for the princely sum of $11.2 billion dollars in 2011, and struck gold in 2013 with its launch of the treatment. Yet, that victory was Gilead's alone, and many Hepatitis C patients, who'd been holding off on treatment in hopes of a better alternative to interferon, found themselves unable to access the promised cure. The unsustainable prices Gilead asked caused payers, both public and private, to institute labyrinthine barriers to treatment for Hepatitis C patients, many of which remain seven years later, despite competition lowering prices. Many state Medicaid programs were flatly unable to afford the drugs at all. Many prison systems found themselves in the same bind, and as a result, some of the most vulnerable people in the United States found themselves with little hope of access.

The high prices spurred a Senate Investigation, one that turned up ethically damning details about Gilead's price-setting process. It showed that Gilead had thought primarily of its own profits, not public health, as it had sought to decide how to price sofosbuvir. It even showed that the earlier discussions had placed sofosbuvir at a third the price eventually chosen, and publicized the IRS grant Pharmasset had received, indicating the involvement of federal money in the drug’s development. But the investigation did not have a broad impact on the access situation. It only secured an

[342] The Price of Solvaldi and its Impact on the United States Health Care System.
[343] Interview with HCV Researcher.

appropriation for the Veterans Administration to afford the drug, neglecting other patients who still needed the drug.

Continued restrictions on access by state Medicaid programs were recognized by the federal government as unlawful, yet, aside from an advisory letter, no federal action was taken to rectify the situation. The state of Louisiana, unable to treat its Hepatitis C patients, turned to the federal government to request §1498 intervention, which would allow the federal government to issue licenses to produce a patented product without the patentholder's permission, be invoked. Despite the considerable precedent set by the use of the law in the 1950s and 1960s, the federal government not only declined to use the law, but actively opposed it, complaining in harmony with the heads of pharmaceutical interest groups that using the law would stifle innovation. Louisiana eventually settled on the Netflix Model of drug procurement, an innovative subscription model.

Though Gilead made remarkable profits in the first years that sofosbuvir was on the market, these revenues declined as competition rose. Business analysts incorrectly attributed this decline to a shrinking patient pool. In reality, only 1 million of the estimated 3.5 million Hepatitis C patients in the United States have been treated with direct acting antiviral regimens. Gilead had prioritized the amount of money it could make from each sale of its products instead of taking into consideration the volume of patients who needed to be treated. By raising the price to a level that constrained volume, it limited its possible profits, and left the market open for its competitors.

Now, facing a pandemic, Gilead seems to have chosen a similar metric for its drug remdesivir, which shows modest promise in treating some cases of COVID-19. After opting to donate 940,000 doses of the drug, Gilead seems poised to make about $9

billion over the next two years.[344] Though the price of remdesivir is a fraction of that of sofosbuvir, it is still high considering the drug's only modest efficacy. No polices have been enacted, no action taken to prevent a repeat of the mistakes made with sofosbuvir.

There were many, many points where meaningful policy, coupled with a willingness to use policy, would have prevented the situation sofosbuvir stumbled into. We're too late to intervene at the root of the problem where sofosbuvir and ledipasvir are concerned. Those mistakes have been made, and patients with the disease that the two drugs promised to cure died because they didn't have the money they needed to save their lives. We can use compulsory licensing now to bring costs down, and use existing federal regulations to bring states like Arizona into line with their legally mandated responsibilities to their Medicaid recipients. But this situation could have been prevented from the start. We are treating the symptoms of a broken system.

U.S.C. §1498 and the Bayh-Dole Act of 1980 have both been discussed as ways to access sofosbuvir. Of the two, §1498 is the more promising. Intended to allow the federal government to infringe upon patents in the interest of the American people while providing "fair compensation" for the patentholder, §1498 has been extensively used since its passage in 1910. It was strengthened in 1942 to protect subcontractors and third parties if they were acting with government authorization. This clarification made it clear that Congress supported the use of the law to produce patented materials without the permission of the patentholder. In the 1960s, Congress again upheld the law's powers in the face of proposed revisions to limit its powers.[345]

---

[344] Boodman, "Gilead Ups Its Donation of the Covid-19 Drug Remdesivir"; Rowland, "Remdesivir May Not Cure Coronavirus, but It's on Track to Make Billions for Gilead."
[345] Brennan et al., "A Prescription for Excessive Drug Pricing."

Widely used by federal government agencies from the Department of Defense to the National Park Service, §1498 was consistently used to procure medications up until the 1970s. Indeed, from 1958 onward, federal entities were encouraged to consider using §1498 even if they were also considering bids to obtain patented items. Procurements of patented drugs from foreign manufacturers based solely on a price advantage over the American patentholders were undertaken and upheld, meaning that if the federal government were to use §1498 to purchase expensive drugs from overseas sources, or to license and manufacture them itself, precedent would be on its side.[346]

The use of §1498 to obtain medications may have fallen out of favor, but it is broadly applicable and has established precedent specifically in the pharmaceutical realm to obtain drugs at a lower price. Invoking §1498 now could increase the access of Medicare, Medicaid, the VA, the Indian Health Service, and the Bureau of Prisons to vitally needed treatments for their beneficiaries. The court costs this may incur are very unlikely to outstrip the money federal agencies already spend on medications. The last time the federal government considered using §1498 was in response to the 2001 anthrax scare to obtain the antibiotic ciprofloxacin from Bayer. Bayer backed down before §1498 was used. The federal government has since declined to consider using its §1498 powers, even in the face of the state of Louisiana's request it be considered. This political reluctance to use a law with such precedence needs to change if we want to adapt to a world where we will not only contend with scourges like Hepatitis C, but also with new diseases like COVID-19.

[346] Brennan et al.

Another reason why §1498 is the most promising option for increasing access to prescription medications is that it is not limited to products that have received federal funding, unlike the Bayh-Dole Act. Bayh-Dole is not as likely a tool to curb drug prices as §1498, but it is worthwhile to spend some time paying attention to the problems the reluctance to enforce its provisions has caused.

Bayh-Dole's march-in rights haven't been used at all. Originally intended to provide incentives to federally-funded inventors while keeping them accountable to the taxpayer, in its realization, Bayh-Dole became the monster its original detractors feared. The onerous bureaucratic process of invoking "march-in", the process by which the federal government can assign a license to ensure the availability of a patented substance whose development it funded, has meant that march-in has never been employed. Because of this reluctance to use the curbs built into the law, patentholders can accept federal money with high confidence that there will be no strings attached. The only thing they need to consider when planning how to market and price an invention is profit. But prioritizing short-term profits when pricing sofosbuvir backfired on Gilead. Payers instituted restriction on Gilead's Hepatitis C drugs, and Gilead's profits declined even as the prevalence of the disease continued to rise.

Additionally, the focus on profit undermines one of the purposes of government funding for innovation. If an innovation, such as a drug, will be profitable when it reaches the market, there is significant incentive for companies and universities to research and patent that drug. But if it won't be profitable, if the disease it treats is too rare, if we are in the middle of an emergency and cannot have access be contingent on profit, or if the research will be insurmountably expensive, it makes sense for the government to step in,

funding the project to lessen the risk and encouraging private entities to fill the gap in the market. To put it in the language of policy researchers, a purpose of government research funding is to correct market failures, and solve problems that the market cannot. The purpose is not to enhance private profit at the expense of public health.

Yet, by declining to hold patentholders accountable to their responsibilities under Bayh-Dole, the federal government has condoned just that. Indeed, a 2013 decision by the National Institutes of Health has rendered it impossible to successfully invoke march-in. In that decision NIH declined to invoke march-in, because there wasn't another company with the patented product already in production, an action that no company would take, because it would open it to litigation from the patentholder. Pricing wasn't an issue in the case of Fabrazyme. But NIH's reluctance to use march-in meant that the Fabrazyme shortage lasted until 2012 and led to preventable deaths. It was an appalling abdication of authority on the part of NIH.[347]

The reluctance to use march-in must end. We must use the Bayh-Dole Act in the way it was intended: not as a blank check for companies, but as a contract stipulating the rights and responsibilities that come with government funding. The reluctance to use march-in rights, even in cases where there is an extreme shortage of the patented material, indicates that funding recipients are not being held accountable to those responsibilities. If a company wishes to patent and make a profit from a product they developed with taxpayer dollars, it must in turn ensure that those very same taxpayers can access that product without undue financial burden, especially if that product can save lives. The benefits must go both ways, not just to the company.

[347] O'Brien, "March-in Rights under the Bayh-Dole Act."

These responsibilities are already a matter of *established law.* But the onerous bureaucratic process of invoking Bayh-Dole's "march-in" has completely dissuaded federal agencies from enforcing those responsibilities, and instead companies have been able to act with, and price with, impunity.

Furthermore, given Bayh-Dole's lack of teeth, underreporting of federal funding on patents is likely common. I say likely, because the database housing information on what entities received federal funding for which products, iEdison, is highly confidential. The public is barred from requesting information from it.[348] This is due to the way in which HHS interprets licensing rights and it means no one is watching the cookie jar. There is no transparency about who got what, aside from the information funding recipients choose to disclose. Without this transparency, we do not know how often companies fail to report government rights in their patents. There is no accountability, merely interesting circumstances, like Pharmasset getting federal funding *only* for prodrugs that never came to market. Nothing can be proven, or disproven, and so nothing can be enforced.

Dodging the responsibilities of Bayh-Dole means selling products for higher prices, focusing on profitable projects at the expense of necessary but commercially uninteresting ones. The motivation for maximizing profits is powerful in the pharmaceutical industry. Drugs are indeed very expensive to make, and lots of them fail before they come to market. Yet, as we have discussed, the majority of the expenditures of drug companies are not, in fact, on R&D. They're not even on marketing! They're on share buybacks, maximizing the profits of the shareholders whose investment determines

[348] Rai and Sampat, "Accountability in Patenting of Federally Funded Research."

the company's value. The disproportionate investment in buybacks undermines the argument that high drug prices are needed to spur innovation. Indeed, it creates the argument that perhaps the motivation of share buybacks is a little too compelling, and the practice ought to be curtailed.

These are the problems of the development pipeline and the early pricing process. Now, let's discuss what should happen once the drug meets the market. The list price of a drug is hardly ever the one that the payers actually pay. That price is usually settled upon after negotiations. But the power of the payer in the United States is severely hampered by the large number of separate payers. By law, Medicare cannot negotiate drug prices, meaning companies can charge them whatever they'd like. Other payers, like private insurance companies, are hampered in another way. They're all competing with each other and therefore have more to lose in a negotiation. If a payer decides a drug is too expensive to cover, and its competitors decide to cover it, it may lose members. The drug company, on the other hand, can walk away and open negotiations with a competing insurance company; it may lose potential patients who stay with the stubborn payer, but those patients may find the lack of coverage a motivation to switch insurance.

Compare this to a single-payer system. If there is a national single-payer system, the drug company has a lot more to lose. It's not going to be able to see the profits from its drug in an entire country if it walks away, losing, potentially, a significant pool of patients. It's therefore much more strongly motivated to price its product at a reasonable level for what it is, since the payer has more power. This is called a monopsony, a counter to the monopoly that a patent grants a drug company.

The switch to a single payer system might be one of the most powerful moves we could possibly make to lower drug prices. It would mean payers, and ultimately, the taxpayer, would have far more ability to negotiate fair prices, because the entity making the decisions would not have to factor its competitors into the process. This strategy has worked well for other countries with universal healthcare. It's very likely it would work well for the United States, if we can overcome the significant monetary barriers to creating a unified system. The downside to this is the likelihood that pharmaceutical profits would drop, which may in turn reduce expenditures on research and development.[349]

High drug prices aren't just due to the actions of a few greedy companies. They are enabled at almost every step by our legal and economic systems, because of the political reluctance to use the laws that were enacted as checks on those systems. The good news is that as soon as the political will exists to use those laws, we have powerful tools to make drugs available. The difficulty will arise in generating that political will.

Is a new miracle drug really a triumph if millions of patients can't get it? Sofosbuvir had, and has, incredible potential to alleviate the suffering of millions. It's a brilliantly designed drug that met a desperate need. But it never got the chance to rise to its true potential. Its price made it stumble before it even got out the gate. Worldwide, only single-digit percentages of Hepatitis C patients have been treated. The gains made in the last few years have been in only a handful of countries able to strike affordable deals with pharmaceutical companies.

---

[349] Dan L. Crippen, *A CBO Analysis of the Administration's Prescription Drug Proposal* (Congressional Budget Office, 2000).

Sofosbuvir could have changed the world for the better. For a fraction of Hepatitis C patients, it *did* change the world for the better. But for everyone else, it's remained as unreachable as if it never existed. Is this really what pharmaceutical success looks like?

I have a response to that question I was asked, over and over, by the researchers at that conference in December, 2019: "What's there to study about Hepatitis C?"

The thing that's left to study about Hepatitis C is why , almost seven years after the approval of sofosbuvir, the disease's prevalence is still rising. Why few patients have been treated. Why treatment refusals from US insurance companies have actually risen. Why existing laws that would have opened up access sat unused as people died of a cured disease. Why "reasonable" business decisions changed a triumph of biochemistry to a public health failure that's continuing even as COVID-19 seizes headlines.

The thing that's left to study about Hepatitis C is why we failed.

REFERENCES

"AbbVie Receives U.S. FDA Approval of Once-Daily VIEKIRA XR™ (Dasabuvir, Ombitasvir, Paritaprevir and Ritonavir) for the Treatment of Genotype 1 Chronic Hepatitis C | AbbVie News Center," July 25, 2016. https://news.abbvie.com/news/abbvie-receives-us-fda-approval-once-daily-viekira-xr-dasabuvir-ombitasvir-paritaprevir-and-ritonavir-for-treatment-genotype-1-chronic-hepatitis-c.htm.

Abdel-Wahab, M. Farid, Soheir Zakaria, Momema Kamel, M. K. Abdel-Khaliq, Mahasen A. Mabrouk, Hosny Salama, Gamal Esmat, David L. Thomas, and G. Thomas Strickland. "High Seroprevalence of Hepatitis C Infection among Risk Groups in Egypt." *The American Journal of Tropical Medicine and Hygiene* 51, no. 5 (November 1, 1994): 563–67. https://doi.org/10.4269/ajtmh.1994.51.563.

Knowledge Ecology International. "About KEI," November 24, 2018. https://www.keionline.org/about.

Aetna. "Hepatitis C - Pharmacy Clinical Policy Bulletins Aetna Non-Medicare Prescription Drug Plan." Aetna, August 6, 2015. http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html.

Al Idrus, Amirah. "'Another Swing, Another Miss' for Gilead as NASH Combo Flops in Phase 2." *FierceBiotech*, December 16, 2019. https://www.fiercebiotech.com/biotech/another-swing-another-miss-for-gilead-as-nash-combo-flops-phase-2.

Alcorn, Ted. "Why Egypt Is at the Forefront of Hepatitis C Treatment." The Atlantic, May 29, 2018. https://www.theatlantic.com/health/archive/2018/05/why-egypt-is-at-the-forefront-of-hepatitis-c-treatment/561305/.

Aleccia, JoNel, Barbara Feder Ostrov, and Donna Gordon Blankinship. "As AbbVie Fights Hepatitis C, States Make Secret Deals with Drugmakers." *USA Today*. Accessed October 25, 2019. https://www.usatoday.com/story/news/health/2019/10/25/abbvie-fights-hepatitis-c-states-make-secret-deals-drugmakers/4087441002/.

Allen, J. Garrott. "Post-Transfusion Hepatitis—A Serious Clinical Problem." *California Medicine* 104, no. 4 (April 1966): 293–99.

Alter, HarveyJ., PaulV. Holland, RobertH. Purcell, and Hans Popper. "TRANSMISSIBLE AGENT IN NON-A, NON-B HEPATITIS." *The Lancet*, Originally

published as Volume 1, Issue 8062, 311, no. 8062 (March 4, 1978): 459–63. https://doi.org/10.1016/S0140-6736(78)90131-9.

American Association for the Study of Liver Diseases, and Infectious Diseases Society of America. “HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C,” May 24, 2018. https://www.hcvguidelines.org/unique-populations/correctional.

Andrade-Filho, José de Souza. “LETTER TO THE EDITOR ANALOGIES IN MEDICINE: WHITE CLAY-PIPE STEM ‘CIRRHOSIS.’” *Revista Do Instituto de Medicina Tropical de São Paulo* 56, no. 1 (2014): 92. https://doi.org/10.1590/S0036-46652014000100016.

Andrews, Keith Bradsher With Edmund L. “A NATION CHALLENGED: CIPRO; U.S. Says Bayer Will Cut Cost of Its Anthrax Drug.” *The New York Times*, October 24, 2001, sec. Business. https://www.nytimes.com/2001/10/24/business/a-nation-challenged-cipro-us-says-bayer-will-cut-cost-of-its-anthrax-drug.html.

Anonymous Provider or Patient Interview, n.d.

Médecins Sans Frontières (MSF) International. “Appeal Lodged against Decision to Uphold Gilead’s Patent on Hepatitis C Drug | MSF.” Accessed January 26, 2020. https://www.msf.org/appeal-lodged-against-decision-uphold-gilead%E2%80%99s-patent-hepatitis-c-drug.

Appleby, Julie. “New Hepatitis C Drugs’ Price Prompts an Ethical Debate: Who Deserves to Get Them?” *Washington Post*, May 2, 2014, sec. Business. https://www.washingtonpost.com/business/new-hepatitis-c-drugs-price-prompts-an-ethical-debate-who-deserves-to-get-them/2014/05/01/73582abc-cfac-11e3-937f-d3026234b51c_story.html.

Arango, María-Teresa, Paula Quintero-Ronderos, John Castiblanco, and Gladis Montoya-Ortíz. *Cell Culture and Cell Analysis*. El Rosario University Press, 2013. https://www.ncbi.nlm.nih.gov/books/NBK459464/.

Arizona Department of Health Services. “AZDHS | Protection from Mosquitoes.” Arizona Department of Health Services. Accessed June 8, 2019. http://www.azdhs.gov/preparedness/epidemiology-disease-control/mosquito-borne/protection-from-mosquitoes/index.php.

Arizona Health Care Cost Containment System. “AHCCCS Medical Policy Manual: Section 320 - Services With Special Circumstances: Hepatitis C Virus (HCV) Prior Authorization Requirements for Direct Acting Antiviral Treatment.” State of Arizona, 7/112018. https://www.azahcccs.gov/shared/Downloads/MedicalPolicyManual/300/320-N.pdf.

Barua, Soumitri, Robert Greenwald, Jason Grebely, Gregory J. Dore, Tracy Swan, and Lynn E. Taylor. “Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States.” *Annals of Internal Medicine* 163, no. 3 (August 4, 2015): 215–23. https://doi.org/10.7326/M15-0406.

Beckman, Adam L., Alyssa Bilinski, Ryan Boyko, George M. Camp, A. T. Wall, Joseph K. Lim, Emily A. Wang, R. Douglas Bruce, and Gregg S. Gonsalves. “New Hepatitis C Drugs Are Very Costly And Unavailable To Many State Prisoners.” *Health Affairs* 35, no. 10 (October 2016): 1893–1901. https://doi.org/10.1377/hlthaff.2016.0296.

Blakinger, Keri. “Texas Inmates Sue for Hepatitis C Drug, Alleging Lack of Treatment Is ‘Cruel and Unusual.’” *Huston Chronicle*, September 18, 2019. https://www.houstonchronicle.com/news/houston-texas/houston/article/Texas-inmates-sue-for-hepatitis-C-drug-alleging-14453099.php.

Boodman, Eric. “Gilead Ups Its Donation of the Covid-19 Drug Remdesivir.” *STAT*, May 19, 2020, sec. Exclusive. https://www.statnews.com/2020/05/18/coronavirus-gilead-ups-remdesivir-donation/.

Brennan, Hannah, Amy Kapczynski, Christine H. Monahan, and Zain Rizvi. “A Prescription for Excessive Drug Pricing: Leveraging Government Patent Use for Health.” *Yale Journal of Law and Technology* 18, no. 1 (April 2, 2017). https://digitalcommons.law.yale.edu/yjolt/vol18/iss1/7.

Brown, Kristen. “Gilead’s Top Management Is Leaving at End of an Era for Biotech.” *Bloomberg*, July 25, 2018. https://www.bloomberg.com/news/articles/2018-07-26/gilead-s-top-management-is-leaving-at-end-of-an-era-for-biotech.

Bryan-Marrugo, O. L., J. Ramos-Jiménez, H. Barrera-Saldaña, A. Rojas-Martínez, R. Vidaltamayo, and A. M. Rivas-Estilla. “History and Progress of Antiviral Drugs: From Acyclovir to Direct-Acting Antiviral Agents (DAAs) for Hepatitis C.” *Medicina Universitaria* 17, no. 68 (July 1, 2015): 165–74. https://doi.org/10.1016/j.rmu.2015.05.003.

Burton, Mary Jane, Kathleen H. Reilly, and Alan Penman. “Incarceration as a Risk Factor for Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-Infection in Mississippi.” *Journal of Health Care for the Poor and Underserved* 21, no. 4 (November 19, 2010): 1194–1202.

Carroll, Rory, and Andrew Chung. “Gilead Ordered to Pay Merck $200 Million in Hepatitis C Drug Patent Dispute - Reuters,” March 24, 2016. https://www.reuters.com/article/us-gilead-sciences-merck-co-damages/gilead-ordered-to-pay-merck-200-million-in-hepatitis-c-drug-patent-dispute-idUSKCN0WR00V.

Carroll, Steven S., David B. Olsen, Malcolm MacCoss, Balkrishen Bhat, Phillip Dan Cook, Anne B. Eldrup, and Thazha P. Prakash. Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase. United States US7105499B2, filed January 18, 2002, and issued September 12, 2006. https://patents.google.com/patent/US7105499B2/en.

Case, P., T. Meehan, and T. S. Jones. "Arrests and Incarceration of Injection Drug Users for Syringe Possession in Massachusetts: Implications for HIV Prevention." *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology: Official Publication of the International Retrovirology Association* 18 Suppl 1 (1998): S71-75.

CDC National Center for Injury Prevention and Control. "2019 Annual Surveillance Report of Drug-Related Risks and Outcomes." Atlanta, Georgia: Centers for Disease Control and Prevention, November 1, 2019. https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf.

Center for Medicaid and CHIP Services. "Assuring Medicaid Beneficiaries Access to Hepatitis C (HCV) Drugs," November 5, 2015. https://www.medicaid.gov/medicaid-chip-program-information/by-topics/prescription-drugs/downloads/rx-releases/state-releases/state-rel-172.pdf.

———. "What's Medicare? | Medicare." Accessed September 1, 2019. https://www.medicare.gov/what-medicare-covers/your-medicare-coverage-choices/whats-medicare.

Center for Medicare and Medicaid Services. "Geographic Variation in Standardized Medicare Spending: County Level," January 2019. https://portal.cms.gov/wps/portal/unauthportal/unauthmicrostrategyreportslink?evt=2048001&src=mstrWeb.2048001&documentID=881776D811E8577F00000080EF85EDD0&visMode=0&currentViewMedia=1&Server=E48V126P&Project=OIPDA-BI_Prod&Port=0&connmode=8&ru=1&share=1&hiddensections=header,path,dockTop,dockLeft,footer.

Centers for Disease Control and Prevention. "2017 Drug Overdose Death Rates | Drug Overdose | CDC Injury Center." Accessed March 15, 2020. https://www.cdc.gov/drugoverdose/data/statedeaths/drug-overdose-death-2017.html.

———. "Hepatitis C Questions and Answers for Health Professionals | CDC," September 10, 2019. https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm.

———. "Hepatitis C Questions and Answers for Health Professionals | CDC." Accessed December 31, 2019. https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1.

———. "Understanding the Epidemic | Drug Overdose | CDC Injury Center," December 19, 2018. https://www.cdc.gov/drugoverdose/epidemic/index.html.

———. “Viral Hepatitis Surveillance - United States, 2016.” Centers for Disease Control and Prevention, 2016.

———. “Yellow Fever: Symptoms, Diagnosis, & Treatment.” Centers for Disease Control and Prevention, January 16, 2019. https://www.cdc.gov/yellowfever/symptoms/index.html.

Chatburn, Robert L., and Eduardo Mireles-Cabodevila. “Chapter 3. Basic Principles of Ventilator Design.” In *Principles and Practice of Mechanical Ventilation*, edited by Martin J. Tobin, 3rd ed. New York, NY: The McGraw-Hill Companies, 2013. accessmedicine.mhmedical.com/content.aspx?aid=57061171.

Choo, Q. L., G. Kuo, A. J. Weiner, L. R. Overby, D. W. Bradley, and M. Houghton. “Isolation of a CDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome.” *Science* 244, no. 4902 (April 21, 1989): 359–62. https://doi.org/10.1126/science.2523562.

Choo, Q. L., K. H. Richman, J. H. Han, K. Berger, C. Lee, C. Dong, C. Gallegos, D. Coit, R. Medina-Selby, and P. J. Barr. “Genetic Organization and Diversity of the Hepatitis C Virus.” *Proceedings of the National Academy of Sciences* 88, no. 6 (March 15, 1991): 2451–55. https://doi.org/10.1073/pnas.88.6.2451.

Clark, Jeremy. CASE NO. 5:09-cv-1789-SLB (UNITED STATES DISTRICT COURT NORTHERN DISTRICT OF ALABAMA NORTHEASTERN DIVISION September 7, 2010).
———. Civil Action No. 08-S-0204-NE (UNITED STATES DISTRICT COURT NORTHERN DISTRICT OF ALABAMA NORTHEASTERN DIVISION December 7, 2008).

———. Civil Action Number 5:10-cv-01487-AKK (UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ALABAMA NORTHEASTERN DIVISION December 20, 2010).

Clark, Jeremy L., Laurent Hollecker, J. Christian Mason, Lieven J. Stuyver, Phillip M. Tharnish, Stefania Lostia, Tamara R. McBrayer, et al. “Design, Synthesis, and Antiviral Activity of 2‘-Deoxy-2‘-Fluoro-2‘-C-Methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication.” *Journal of Medicinal Chemistry* 48, no. 17 (August 1, 2005): 5504–8. https://doi.org/10.1021/jm0502788.

Cohen, Jon. “King of the Pills.” *Science* 348, no. 6235 (May 8, 2015): 622–25. https://doi.org/10.1126/science.348.6235.622.

Coll, Steve. “The Jail Health-Care Crisis,” New Yorker, February 25, 2019. https://www.newyorker.com/magazine/2019/03/04/the-jail-health-care-crisis.

Cope, Rebecca, Thomas Glowa, Samantha Faulds, Deborah McMahon, and Ramakrishna Prasad. “Treating Hepatitis C in a Ryan White-Funded HIV Clinic: Has the Treatment Uptake Improved in the Interferon-Free Directly Active Antiviral Era?” *AIDS Patient Care & STDs* 30, no. 2 (February 2016): 51–55. https://doi.org/10.1089/apc.2015.0222.
“Corporate History Timeline | Gilead.” Accessed April 3, 2019. https://www.gilead.com/about/corporate-history.

Crippen, Dan L. *A CBO Analysis of the Administration’s Prescription Drug Proposal*. Congressional Budget Office, 2000.

“CV_Ralf-Bartenschlager.Pdf.” Accessed July 22, 2019. https://www.dkfz.de/en/virus-assoziierte-karzinogenese/groups/AGBartenschlager/CV_Ralf-Bartenschlager.pdf?m=1487759647.

Deegan, Gordon. “Profits Soar at Irish Arm of Gilead Even as Revenues Decline.” *The Irish Times*, December 5, 2019. https://www.irishtimes.com/business/health-pharma/profits-soar-at-irish-arm-of-gilead-even-as-revenues-decline-1.4106163.
Science Direct Topics. “DNA Polymerase - an Overview.” Accessed July 19, 2019. https://www.sciencedirect.com/topics/neuroscience/dna-polymerase.

Douglass, Michael. “Has Gilead Sciences’ Cash Cow Finally Hit Bottom?” *The Motley Fool* (blog), January 23, 2017. https://www.fool.com/investing/2017/01/23/has-gilead-sciences-cash-cow-finally-hit-bottom.aspx.

———. “I Was Wrong About Gilead Sciences -.” *The Motley Fool* (blog), March 9, 2017. https://www.fool.com/investing/2017/03/09/i-was-wrong-about-gilead-sciences.aspx.

El-Sayed, Manal. “Elimination of HCV in Egypt: A Global Model.” In *Confrence Proceedings from HepDART 2019*, Vol. 1. Tucker, GA: Global Hepatitis Journal, 2019. https://informedhorizonseducation.com/scientific-program?utm_term=0_73d2edd14c-8126873a32-66369597.

Epstein, Steven. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. 1st ed. Berkeley and Los Angeles, California: University of California Press, 1998. https://www.ucpress.edu/book/9780520214453/impure-science.
Exercise of march-in rights, 37 CFR § 201e (2002).

Facher, Lev. “Study Shows Purdue’s Switch to ‘abuse-Deterrent’ OxyContin Helped Drive a Spike in Hepatitis C Infections.” *Stat News*, February 4, 2019.
Farmer, Paul. *Infections and Inequalities: The Modern Plagues*. University of California Press, 2001.

———. “The Global AIDS Response Can Help in Fighting Hepatitis C.” *Washington Post*, February 12, 2014, sec. Opinions. https://www.washingtonpost.com/opinions/the-global-aids-response-can-help-in-fighting-hepatitis-c/2014/02/12/aa76ecc2-89e3-11e3-833c-33098f9e5267_story.html.

The Henry J. Kaiser Family Foundation. “Federal and State Share of Medicaid Spending,” October 11, 2018. https://www.kff.org/medicaid/state-indicator/federalstate-share-of-spending/.

Feitelson, Mark A. *Hepatitis C Virus: From Laboratory to Clinic*. Cambridge, UNITED KINGDOM: Cambridge University Press, 2002. http://ebookcentral.proquest.com/lib/asulib-ebooks/detail.action?docID=201762.

Fentem, Sarah. “Appeals Court Upholds Class Action Status for Thousands of Missouri Inmates with Hepatitis,” December 6, 2018. https://news.stlpublicradio.org/post/appeals-court-upholds-class-action-status-thousands-missouri-inmates-hepatitis.

FIELDS v. CORIZON HEALTH, | Case No. 2:09-cv-529... | 20120120987| Leagle.com (United States District Court, M.D. Florida, Fort Myers Division January 19, 2012).

Fioretti, Maria C., Marina Liberati, Enzo Bonmassar, and Gustavo Cudkowicz. “Immune Inhibition of Allogeneic Lymphoma Cells in the Peritoneal Cavity of Mice.” *Cancer Research* 35, no. 1 (January 1, 1975): 30–36.

Flournoy, Blake. “What Is Serum?” Sciencing, July 20, 2018. https://sciencing.com/what-is-serum-4673561.html.

Friedman, Robert M., and Sara Contente. “Treatment of Hepatitis C Infections with Interferon: A Historical Perspective.” *Hepatitis Research and Treatment* 2010 (2010). https://doi.org/10.1155/2010/323926.

Galea, Sandro, and David Vlahov. “Social Determinants and the Health of Drug Users: Socioeconomic Status, Homelessness, and Incarceration.” *Public Health Reports (1974-)* 117 (2002): S135–45.

Gee, Alistair. “Lives Cut Short: Remembering Health Care Workers In Their 20s Killed By COVID-19.” *NPR.Org*, August 13, 2018. https://www.npr.org/sections/health-shots/2020/08/13/901720066/lives-cut-short-remembering-health-care-workers-in-their-20s-killed-by-covid-19.

Gee, Rebekah. “Louisiana’s Journey Toward Eliminating Hepatitis C | Health Affairs.” *Health Affairs Blog* (blog), April 1, 2019. https://www.healthaffairs.org/do/10.1377/hblog20190327.603623/full/.

Gibbons, Ann. “Bonobos Join Chimps as Closest Human Relatives.” *Science | AAAS*, June 13, 2012. https://www.sciencemag.org/news/2012/06/bonobos-join-chimps-closest-human-relatives.

Gilead. “Gilead Sciences to Acquire Triangle Pharmaceuticals for $464 Million | Gilead.” December 4, 2002. https://www.gilead.com/news/press-releases/2002/12/gilead-sciences-to-acquire-triangle-pharmaceuticals-for-464-million.

Clinical Trials Arena. “Gilead Combination Therapy for NASH Misses Primary Phase II Trial Goal,” December 17, 2019. https://www.clinicaltrialsarena.com/news/gilead-nash-trial-atlas-fails/.

“Gilead Could Have Had Pharmasset Cheap: Founder.” *Reuters*, November 22, 2011. https://www.reuters.com/article/us-pharmasset-founder/gilead-could-have-had-pharmasset-cheap-founder-idUSTRE7AL2ES20111122.

Gilead Sciences. “Gilead Subsidiary to Launch Authorized Generics of Epclusa® (Sofosbuvir/Velpatasvir) and Harvoni® (Ledipasvir/Sofosbuvir) for the Treatment of Chronic Hepatitis C.” Accessed October 15, 2019. https://www.gilead.com/news-and-press/press-room/press-releases/2018/9/gilead-subsidiary-to-launch-authorized-generics-of-epclusa-sofosbuvirvelpatasvir-and-harvoni-ledipasvirsofosbuvir-for-the-treatment-of-chronic.

“Gilead Sciences - SourceWatch.” Accessed April 3, 2019. https://www.sourcewatch.org/index.php/Gilead_Sciences.

“Gilead Sciences Announces Fourth Quarter and Full Year 2019 Financial Results.” Accessed October 7, 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/2/gilead-sciences-announces-fourth-quarter-and-full-year-2019-financial-results.

“Gilead Sciences Announces Second Quarter 2019 Financial Results,” July 30, 2019. https://www.gilead.com/news-and-press/press-room/press-releases/2019/7/gilead-sciences-announces-second-quarter-2019-financial-results.

Gilead Sciences, INC. v. Merck & Co. INC., Merck Sharp & Dohme Corp., Ionis Pharmaceuticals, INC. (United States District Court for the Northern District of California April 25, 2018).

Americans For Tax Fairness. “Gilead Sciences: Price Gouger, Tax Dodger,” July 13, 2016. https://americansfortaxfairness.org/new-report-gilead-sciences-price-gouger-tax-dodger/.

Gowda, Charitha, Stephen Lott, Matthew Grigorian, Dena M. Carbonari, M. Elle Saine, Stacey Trooskin, Jason A. Roy, Jay R. Kostman, Paul Urick, and Vincent Lo Re.

"Absolute Insurer Denial of Direct-Acting Antiviral Therapy for Hepatitis C: A National Specialty Pharmacy Cohort Study." *Open Forum Infectious Diseases* 5, no. 6 (June 1, 2018). https://doi.org/10.1093/ofid/ofy076.

Grebely, Jason, Julie Bruneau, Philip Bruggmann, Magdalena Harris, Matthew Hickman, Tim Rhodes, and Carla Treloar. "Elimination of Hepatitis C Virus Infection among PWID: The Beginning of a New Era of Interferon-Free DAA Therapy." *International Journal of Drug Policy* 47 (September 1, 2017): 26–33. https://doi.org/10.1016/j.drugpo.2017.08.001.

Haseltine, William A. "The Other Shoe Drops: Gilead's Outrageous Pricing Of Remdesivir." *Forbes*, June 29, 2020, sec. Innovation. https://www.forbes.com/sites/williamhaseltine/2020/06/29/the-other-shoe-drops-gileads-outrageous-pricing-of-remdesivir/.

Health Resources & Services Administration. "Who Was Ryan White?" Text. HRSA Ryan White HIV/AIDS Program, August 9, 2016. https://hab.hrsa.gov/about-ryan-white-hivaids-program/who-was-ryan-white.

Helfand, Carly. "Sovaldi Forces Incivek off the Hep C Market as Vertex Calls It Quits | FiercePharma," August 13, 2014. https://www.fiercepharma.com/sales-and-marketing/sovaldi-forces-incivek-off-hep-c-market-as-vertex-calls-it-quits.

"Hepatitis C Guidance: AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected with Hepatitis C Virus." *Hepatology* 62, no. 3 (September 1, 2015): 932–54. https://doi.org/10.1002/hep.27950.

"Hepatitis C: State of Medicaid Access Report Card." Center for Health Law and Policy Innovation Harvard Law School, 2017.

"Hepatitis C Virus." In *Wikipedia*, July 11, 2020. https://en.wikipedia.org/w/index.php?title=Hepatitis_C_virus&oldid=967091076.

Hézode, Christophe, Nicole Forestier, Geoffrey Dusheiko, Peter Ferenci, Stanislas Pol, Tobias Goeser, Jean-Pierre Bronowicki, et al. "Telaprevir and Peginterferon with or without Ribavirin for Chronic HCV Infection." *New England Journal of Medicine* 360, no. 18 (April 30, 2009): 1839–50. https://doi.org/10.1056/NEJMoa0807650.
"History of Gilead Sciences, Inc. – FundingUniverse." Accessed April 3, 2019. http://www.fundinguniverse.com/company-histories/gilead-sciences-inc-history/.

Hoffman, Jan. "Johnson & Johnson Ordered to Pay $572 Million in Landmark Opioid Trial." *The New York Times*, August 26, 2019, sec. Health. https://www.nytimes.com/2019/08/26/health/oklahoma-opioids-johnson-and-johnson.html.

———. “Purdue Pharma and Sacklers Reach $270 Million Settlement in Opioid Lawsuit.” *The New York Times*, March 26, 2019, sec. Health. https://www.nytimes.com/2019/03/26/health/opioids-purdue-pharma-oklahoma.html.

Hollinger, Blaine, Gary L. Gitnick, Richard D. Aach, Wolf Szmuness, James W. Mosley, Cladd E. Stevens, Robert L. Peters, John M. Weiner, Jochewed B. Werch, and Jerrold J. Lander. “Non-A, Non-B Hepatitis Transmission in Chimpanzees: A Project of the Transfusion-Transmitted Viruses Study Group.” *Intervirology* 10, no. 1 (1978): 60–68. https://doi.org/10.1159/000148969.

Houghton, Michael, Amy Weiner, Jang Han, George Kuo, and Qui-Lim Choo. “Molecular Biology of the Hepatitis C Viruses: Implications for Diagnosis, Development and Control of Viral Disease.” *Hepatology* 14, no. 2 (1991): 381–388.

HealthCare.gov. “How Medicaid Health Care Expansion Affects You.” General Information. Accessed September 2, 2019. https://www.healthcare.gov/medicaid-chip/medicaid-expansion-and-you/.

Indian Health Service. “Disparities | Fact Sheets.” *Indian Health Service Newsroom*, January 1, 2013. https://www.ihs.gov/newsroom/factsheets/disparities/.

———. “Indian Health Service Highlights Initiative to Eliminate Hepatitis C and HIV/AIDS in Indian Country during National Native HIV/AIDS Awareness Day | 2019 Press Releases.” *Indian Health Service Newsroom*, March 19, 2019. https://www.ihs.gov/newsroom/pressreleases/2019pressreleases/indian-health-service-highlights-initiative-to-eliminate-hepatitis-c-and-hiv-aids-in-indian-country-during-national-native-hiv-aids-awareness-day/.

Interview with HCV Researcher, n.d.

Jan, Tracy. “After Prison, a Lifetime of Economic Punishment.” *Washington Post*, September 3, 2019. https://www.washingtonpost.com/graphics/2019/business/jobs-after-prison-rhode-island-recently-occupational-licensing/.

January 5, Transplanted ·, and 2016. “The Wyden-Grassley US Senate Investigation Into The Pricing Of Sovaldi: A Report Part I.” *HepatitisC.Net* (blog), January 5, 2016. https://hepatitisc.net/living/us-senate-sovaldi-part-i/.

———. “The Wyden-Grassley US Senate Investigation Into The Pricing Of Sovaldi: A Report Part I.” *HepatitisC.Net* (blog), January 5, 2016. https://hepatitisc.net/living/us-senate-sovaldi-part-i/.

Japsen, Bruce. “As Pricey Hepatitis Pill Harvoni Joins Sovaldi, States Erect Medicaid Hurdles.” *Forbes*, October 10, 2014.

https://www.forbes.com/sites/brucejapsen/2014/10/10/as-hepatitis-pill-harvoni-joins-sovaldi-states-erect-medicaid-hurdles/.

Johnson, Carolyn Y. “Louisiana Considers Radical Step to Counter High Drug Prices: Federal Intervention.” *Washington Post*, July 3, 2017. https://www.washingtonpost.com/business/economy/louisiana-considers-radical-step-to-counter-high-drug-prices-federal-intervention/2017/07/03/456b99f6-4a59-11e7-a186-60c031eab644_story.html.

Johnson, Charles, and Vertex Pharmaceuticals Incorporated. “Discontinuation of INCIVEK® (Telaprevir) Tablets in the United States,” August 11, 2014. http://freepdfhosting.com/f75f8bac14.pdf.

Joudrey, Paul J., Maria R. Khan, Emily A. Wang, Joy D. Scheidell, E. Jennifer Edelman, D. Keith McInnes, and Aaron D. Fox. “A Conceptual Model for Understanding Post-Release Opioid-Related Overdose Risk.” *Addiction Science & Clinical Practice* 14, no. 1 (April 15, 2019): 17. https://doi.org/10.1186/s13722-019-0145-5.

Kapczynski, Amy, and Aaron S. Kesselheim. “‘Government Patent Use’: A Legal Approach To Reducing Drug Spending.” *Health Affairs* 35, no. 5 (May 1, 2016): 791–97. https://doi.org/10.1377/hlthaff.2015.1120.

Karimi, Faith. “The Maker of OxyContin Insists It’s Not to Blame for the Opioid Epidemic.” *CNN*, June 20, 2019. https://www.cnn.com/2019/06/20/health/purdue-pharma-david-sackler-vanity-fair/index.html.

Kim, Tae. “Goldman Asks: ‘Is Curing Patients a Sustainable Business Model?’” *CNBC*, April 11, 2018. https://www.cnbc.com/2018/04/11/goldman-asks-is-curing-patients-a-sustainable-business-model.html.

Kingston, William. “Antibiotics, Invention and Innovation.” *Research Policy* 29, no. 6 (June 1, 2000): 679–710. https://doi.org/10.1016/S0048-7333(99)00045-1.

Kliff, Sarah. “The True Story of America’s Sky-High Prescription Drug Prices.” *Vox*, November 30, 2016. https://www.vox.com/science-and-health/2016/11/30/12945756/prescription-drug-prices-explained.

Knowledge Ecology International. “U.S. Patent 7,964,580,” 2018.

Kohli, Anita, Ashton Shaffer, Amy Sherman, and Shyam Kottilil. “Treatment of Hepatitis C: A Systematic Review.” *JAMA* 312, no. 6 (August 13, 2014): 631–40. https://doi.org/10.1001/jama.2014.7085.

Kulish, Nicholas, Sarah Kliff, and Jessica Silver-Greenberg. “The U.S. Tried to Build a New Fleet of Ventilators. The Mission Failed.” *The New York Times*, March 29, 2020,

sec. Business. https://www.nytimes.com/2020/03/29/business/coronavirus-us-ventilator-shortage.html.

Lai, Ching-Lung, and Man-Fung Yuen. “Chronic Hepatitis B — New Goals, New Treatment.” *New England Journal of Medicine* 359, no. 23 (December 4, 2008): 2488–91. https://doi.org/10.1056/NEJMe0808185.

Lam, Angela M., Eisuke Murakami, Christine Espiritu, Holly M. Micolochick Steuer, Congrong Niu, Meg Keilman, Haiying Bao, et al. “PSI-7851, a Pronucleotide of β-d-2′-Deoxy-2′-Fluoro-2′-C-Methyluridine Monophosphate, Is a Potent and Pan-Genotype Inhibitor of Hepatitis C Virus Replication.” *Antimicrobial Agents and Chemotherapy* 54, no. 8 (August 1, 2010): 3187–96. https://doi.org/10.1128/AAC.00399-10.

Leston, Jessica, and Joe Finkbonner. “The Need to Expand Access to Hepatitis C Virus Drugs in the Indian Health Service.” *JAMA* 316, no. 8 (August 23, 2016): 817. https://doi.org/10.1001/jama.2016.7186.

Liang, T. Jake, and John W. Ward. “Hepatitis C in Injection-Drug Users — A Hidden Danger of the Opioid Epidemic.” *New England Journal of Medicine* 378, no. 13 (March 29, 2018): 1169–71. https://doi.org/10.1056/NEJMp1716871.

Liu, Peng, Ashoke Sharon, and Chung K Chu. “Fluorinated Nucleosides: Synthesis and Biological Implication.” *Journal of Fluorine Chemistry* 129, no. 9 (September 2008): 743–66. https://doi.org/10.1016/j.jfluchem.2008.06.007.

Lopes, Lunna, Bryan Wu, and 2019. “KFF Health Tracking Poll – February 2019: Prescription Drugs.” *The Henry J. Kaiser Family Foundation* (blog), March 1, 2019. https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-february-2019-prescription-drugs/.

Los Angeles Department of Public Health. “Hepatitis A Outbreak in Los Angeles County,” September 19, 2017. http://publichealth.lacounty.gov/acd/Diseases/HepA.htm.

Lovelace Jr., Berkeley. “Nearly Every US State Is Now Suing OxyContin Maker Purdue Pharma.” *CNBC*, June 4, 2019. https://www.cnbc.com/2019/06/04/nearly-every-us-state-is-now-suing-oxycontin-maker-purdue-pharma.html.

Lupkin, Sydney. “A Decade Marked By Outrage Over Drug Prices.” *NPR.Org*, December 31, 2019. https://www.npr.org/sections/health-shots/2019/12/31/792617538/a-decade-marked-by-outrage-over-drug-prices.

———. “FDA Grants Experimental Coronavirus Drug Benefits For Rare Disease Treatments.” *NPR.Org*, March 24, 2020. https://www.npr.org/sections/health-shots/2020/03/24/821035311/fda-grants-experimental-coronavirus-drug-benefits-for-rare-disease-treatments.

———. “Remdesivir Priced At More Than $3,100 For A Course Of Treatment.” *NPR.Org*, June 29, 2020. https://www.npr.org/sections/health-shots/2020/06/29/884648842/remdesivir-priced-at-more-than-3-100-for-a-course-of-treatment.

Ma, Han, Wen-Rong Jiang, Nicole Robledo, Vincent Leveque, Samir Ali, Teresa Lara-Jaime, Mohammad Masjedizadeh, et al. “Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor β-d-2′-Deoxy-2′-Fluoro-2′-C-Methylcytidine (PSI-6130) and Identification of a Novel Active 5′-Triphosphate Species.” *Journal of Biological Chemistry* 282, no. 41 (October 12, 2007): 29812–20. https://doi.org/10.1074/jbc.M705274200.

Macy, Beth. *Dopesick: Dealers, Doctors, and the Drug Company That Addicted America*. Little, Brown, 2018.

Mahmoud Mourad, and Lena Masri. “Millions Flock to Free Tests as Egypt Seeks to Eradicate Hepatitis C - Reuters.” Accessed February 3, 2020. https://www.reuters.com/article/us-health-egypt-hepatitis-c/millions-flock-to-free-tests-as-egypt-seeks-to-eradicate-hepatitis-c-idUSKBN1O21IO.

Marso, Andy. “Locked out of Care: Brain Fungus Death Points to Extensive Problems in Kansas Prisons.” *Kansas City Star*, April 28, 2019. https://www.kansascity.com/news/business/health-care/article229423849.html.

Martin, John C., Michael J. M. Hitchcock, Erik De Clercq, and William H. Prusoff. “Early Nucleoside Reverse Transcriptase Inhibitors for the Treatment of HIV: A Brief History of Stavudine (D4T) and Its Comparison with Other Dideoxynucleosides.” *Antiviral Research*, Twenty-five Years of Antiretroviral Drug Development: Progress and Prospects, 85, no. 1 (January 1, 2010): 34–38. https://doi.org/10.1016/j.antiviral.2009.10.006.

Mayo Clinic. “Liver Biopsy.” Mayo Clinic. Accessed April 2, 2019. https://www.mayoclinic.org/tests-procedures/liver-biopsy/about/pac-20394576.

McCoy, Michael. “Gilead and Galapagos Strike Big R&D Deal.” *Chemical & Engineering News*, July 15, 2019. https://cen.acs.org/business/mergers-&-acquisitions/Gilead-Galapagos-strike-big-RD/97/web/2019/07.

Medecins Sans Frontieres. “Hepatitis C - Not Even Close.” Issue Brief, October 29, 2017. https://msfaccess.org/hepatitis-c-not-even-close.

Meier, Barry. “In Guilty Plea, OxyContin Maker to Pay $600 Million.” *The New York Times*, May 10, 2007, sec. Business Day. http://www.nytimes.com/2007/05/10/business/11drug-web.html.

Mello, Patricia Campos. “Cost of Hepatitis C Drug Price Skyrockets 1,422% after Patent Approval.” *Folha de S.Paulo*, October 22, 2019. https://www1.folha.uol.com.br/internacional/en/scienceandhealth/2019/10/cost-of-hepatitis-c-drug-price-skyrockets-1422-after-patent-approval.shtml.

Merck. “Merck Press Release: FDA Approves Merck’s VICTRELIS (Boceprevir), First-in-Class Oral Hepatitis C Virus (HCV) Protease Inhibitor.” Accessed September 30, 2019. http://www.natap.org/2011/HCV/051811_05.htm.

IPWatchdog.com | Patents & Patent Law. “Merck Hepatitis C Virus Treatment Patents Unenforceable Due to Unclean Hands,” May 7, 2018. http://www.ipwatchdog.com/2018/05/07/merck-hcv-treatment-patents-unenforceable/id=96509/.

“Merck Loses Bid to Revive $200 Million Gilead Verdict at U.S. High...” *Reuters*, January 7, 2019. https://www.reuters.com/article/us-usa-court-merck-idUSKCN1P11G5.

Miller, F. DeWolfe, and Laith J. Abu-Raddad. “Evidence of Intense Ongoing Endemic Transmission of Hepatitis C Virus in Egypt.” *Proceedings of the National Academy of Sciences* 107, no. 33 (August 17, 2010): 14757–62. https://doi.org/10.1073/pnas.1008877107.

Mishra, Manas, and Michael Erman. “Gilead Asks FDA to Take Back Lucrative Orphan Drug Status on Possible Coronavirus Treatment.” *Reuters*, March 25, 2020. https://www.reuters.com/article/us-health-coronavirus-gilead-sciences-idUSKBN21C3MG.

Mohamed, Mostafa K., Mohamed Abdel-Hamid, Nabiel N. Mikhail, Fatma Abdel-Aziz, Ahmed Medhat, Laurence S. Magder, Alan D. Fix, and G. Thomas Strickland. “Intrafamilial Transmission of Hepatitis C in Egypt.” *Hepatology* 42, no. 3 (September 1, 2005): 683–87. https://doi.org/10.1002/hep.20811.

Moriarty, Erin. “Scientist Forms New Firm.” *Atlanta Business Chronicle*, August 8, 2005. https://www.bizjournals.com/atlanta/stories/2005/08/08/story1.html.

Mourad, Mahmoud, and Lena Masri. “Millions Flock to Free Tests as Egypt Seeks to Eradicate Hepatitis C.” *Reuters*, December 3, 2018. https://www.reuters.com/article/us-health-egypt-hepatitis-c-idUSKBN1O21IO.

Moyer, Andrew J., and Robert D. Coghill. “Penicillin.” *Journal of Bacteriology* 51, no. 1 (January 1946): 79–93.

Doctors Without Borders - USA. “MSF Challenges Gilead’s Undeserved Patent on Hepatitis C Drug in China,” June 19, 2018. https://www.doctorswithoutborders.org/what-

we-do/news-stories/news/msf-challenges-gileads-undeserved-patent-hepatitis-c-drug-china.

Doctors Without Borders - USA. “MSF: USTR Special 301 Report Calls Out Countries for Protecting Public Health,” April 27, 2018. https://www.doctorswithoutborders.org/what-we-do/news-stories/news/msf-ustr-special-301-report-calls-out-countries-protecting-public.

Murakami, Eisuke, Tatiana Tolstykh, Haiying Bao, Congrong Niu, Holly M. Micolochick Steuer, Donghui Bao, Wonsuk Chang, et al. “Mechanism of Activation of PSI-7851 and Its Diastereoisomer PSI-7977.” *Journal of Biological Chemistry* 285, no. 45 (November 5, 2010): 34337–47. https://doi.org/10.1074/jbc.M110.161802.

National Academy of Sciences (US) Committee on Criteria for Federal Support of Research and Development. *Supplement 1: The Evolution and Impact of Federal Government Support for R&D in Broad Outline*. *Allocating Federal Funds for Science and Technology*. National Academies Press (US), 1995. https://www.ncbi.nlm.nih.gov/books/NBK45556/.

National Institutes of Health. “Budget | National Institutes of Health (NIH).” National Institutes of Health (NIH), June 29, 2020. https://www.nih.gov/about-nih/what-we-do/budget.

Neushul, Peter. “Science, Government and the Mass Production of Penicillin.” *Journal of the History of Medicine and Allied Sciences* 48, no. 4 (October 1, 1993): 371–95. https://doi.org/10.1093/jhmas/48.4.371.

“New HCV Nucleotide Polymerase PSI-7851 Achieves 1 Log Reduction in Viral Load in 3-Day Study,” 2009. http://www.natap.org/2009/HCV/080109_01.htm.

O’Brien, William. “March-in Rights under the Bayh-Dole Act: The NIH’s Paper Tiger.” *Seton Hall Law Review* 43 (2013): 1403.

“Opioid Patient Worth $200,000 a Year to Purdue, State Says.” *Bloomberg.Com*, August 2, 2019. https://www.bloomberg.com/news/articles/2019-08-02/sacklers-are-massachusetts-ag-s-opioid-scapegoat-lawyer-says.

Orlewicz, Marc S. “Alanine Aminotransferase: Reference Range, Interpretations, Collection and Panels,” December 13, 2018. https://emedicine.medscape.com/article/2087247-overview.

Owens, Jeremy C. “Gilead Earnings Show Surprising Sales Increase amid Massive Change.” MarketWatch. Accessed February 4, 2020. https://www.marketwatch.com/story/gilead-earnings-show-surprising-sales-increase-amid-massive-change-2019-07-30.

Patel, Manish, Saira Rab, Aley G. Kalapila, Alison Kyle, Ike Solomon Okosun, and Lesley Miller. “Highly Successful Hepatitis C Virus (HCV) Treatment Outcomes in Human Immunodeficiency Virus/HCV-Coinfected Patients at a Large, Urban, Ryan White Clinic.” *Open Forum Infectious Diseases* 4, no. 2 (April 5, 2017). https://doi.org/10.1093/ofid/ofx062.

“Pharmasset Nominates PSI-7851 as a Lead Development Candidate for the Treatment of Chronic Hepatitis C.” Accessed August 2, 2019. http://www.natap.org/2008/HCV/051908_02.htm.

Philips. “Philips Introduces New Philips Respironics E30 Ventilator to Help Free up ICU Units in Wake of COVID-19,” April 14, 2020. https://www.philips.com/a-w/about/news/archive/standard/news/articles/2020/20200414-philips-introduces-new-philips-respironics-e30-ventilator-to-help-free-up-icu-units-in-wake-of-covid-19.html.

Pollack, Andrew. “Drug Goes From $13.50 a Tablet to $750, Overnight.” *The New York Times*, September 20, 2015, sec. Business. https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html.

———. “Sales of Sovaldi, New Gilead Hepatitis C Drug, Soar to $10.3 Billion.” *The New York Times*, January 10, 2018, sec. Business. https://www.nytimes.com/2015/02/04/business/sales-of-sovaldi-new-gilead-hepatitis-c-drug-soar-to-10-3-billion.html.

Poonia, Bhawna, and Shyam Kottilil. “Newer Therapeutics for Hepatitis C.” *Annals of Translational Medicine* 4, no. 2 (January 2016). https://doi.org/10.3978/j.issn.2305-5839.2015.10.06.

POWELL, J.M., Kenneth R. Foster, Mary F. Jenkins, and Anna Coxe Toogood. *Bring Out Your Dead: The Great Plague of Yellow Fever in Philadelphia in 1793*. University of Pennsylvania Press, 1993. https://www.jstor.org/stable/j.ctt6wr9c9.

Press, Associated. “Hepatitis C ‘Cure’ Costs $1,000, Double the Intended Price.” *New York Post* (blog), July 29, 2014. https://nypost.com/2014/07/29/hepatitis-c-cure-costs-1000-double-the-intended-price/.

Prince, AlfredM, GeorgeF Grady, Charles Hazzi, Betsy Brotman, WilliamJ Kuhns, RichardW Levine, and StephenJ Millian. “LONG-INCUBATION POST-TRANSFUSION HEPATITIS WITHOUT SEROLOGICAL EVIDENCE OF EXPOSURE TO HEPATITIS-B VIRUS.” *The Lancet*, Originally published as Volume 2, Issue 7875, 304, no. 7875 (August 3, 1974): 241–46. https://doi.org/10.1016/S0140-6736(74)91412-3.

Quammen, David. *Spillover : Animal Infections and the next Human Pandemic*. 1st ed.. New York: W.W. Norton & Co., 2012.

Rai, Arti, and Bhaven Sampat. "Accountability in Patenting of Federally Funded Research." *Nature Biotechnology* 30, no. 10 (January 1, 2012): 953–56.

Raymond, Nate. "Oklahoma Judge to Rule on Monday in Opioid Lawsuit against J&J." *Reuters*, August 22, 2019. https://www.reuters.com/article/us-usa-opioids-litigation-oklahoma-idUSKCN1VB1TO.

Re, Vincent Lo, Charitha Gowda, Paul N. Urick, Joshua T. Halladay, Amanda Binkley, Dena M. Carbonari, Kathryn Battista, et al. "Disparities in Absolute Denial of Modern Hepatitis C Therapy by Type of Insurance." *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association* 14, no. 7 (July 2016): 1035–43. https://doi.org/10.1016/j.cgh.2016.03.040.

Reuters. "Merck Wins Hepatitis C Drug Patent Claim Against Gilead." *The New York Times*, March 22, 2016, sec. Business. https://www.nytimes.com/2016/03/23/business/merck-wins-hepatitis-c-drug-patent-claim-against-gilead.html.

Review, Technology. "Medicine's Manhattan Project." MIT Technology Review. Accessed January 3, 2020. https://www.technologyreview.com/s/400443/medicines-manhattan-project/.

Robbins, Stanley L. *Textbook of Pathology With Clinical Application*. Second Edition. Philadelphia: W. B. Saunders Company, 1962.

Rotella, Sebastian, and Patricia Callahan. "Taxpayers Paid Millions to Design a Low-Cost Ventilator for a Pandemic. Instead, the Company Is Selling Versions of It Overseas." *ProPublica*. March 30, 2020. Https://www.propublica.org/. https://www.propublica.org/article/taxpayers-paid-millions-to-design-a-low-cost-ventilator-for-a-pandemic-instead-the-company-is-selling-versions-of-it-overseas-.

Rowland, Christopher. "Remdesivir May Not Cure Coronavirus, but It's on Track to Make Billions for Gilead." *Washington Post*, October 30, 2020. https://www.washingtonpost.com/business/2020/09/30/remdesivir-drug-coronavirus-gilead/.

Roy, Victor, and Lawrence King. "Betting on Hepatitis C: How Financial Speculation in Drug Development Influences Access to Medicines." *BMJ : British Medical Journal (Online); London* 354 (July 27, 2016). http://dx.doi.org.ezproxy1.lib.asu.edu/10.1136/bmj.i3718.

Rubin, Richard. “Companies Save Billions in Taxes by Shifting Assets Around Globe.” *Wall Street Journal*, April 8, 2020, sec. US. https://www.wsj.com/articles/companies-save-billions-in-taxes-by-shifting-assets-around-globe-11586347201.

Saphir, Ann, and Howard Schneider. “Fed Chief Says Coronavirus Surge Slowing U.S. Economic Recovery.” *Reuters*, July 29, 2020. https://www.reuters.com/article/us-usa-fed-idUSKCN24U2VB.

Schinazi, Raymond F., and Dennis C. Liotta. Compositions containing 5-fluoro-2’,3’-didehydro-2’,3’-dideoxycytidine or a mono-, di-, or triphosphate thereof and a second antiviral agent. United States US5703058A, filed January 27, 1995, and issued December 30, 1997. https://patents.google.com/patent/US5703058A/en.

Schinazi, Raymond F., Dennis C. Liotta, Chung K. Chu, J. Jeffrey McAtee, Junxing Shi, Yongseok Choi, Kyeong Lee, and Joon H. Hong. 2′-Fluoronucleosides. United States, filed February 25, 1999, and issued February 19, 2002. https://patents.google.com/patent/US6348587B1/en.

———. 2′-Fluoronucleosides. United States US7307065B2, filed March 8, 2004, and issued December 11, 2007. https://patents.google.com/patent/US7307065/en?oq=schnazi+patent+fluoro+nucleosides+1999.

Knowledge Ecology International. “Secretary Alex Azar’s Comment on 28 USC 1498 Submitted for the Record of the 2018 Confirmation Hearings,” August 1, 2018. https://www.keionline.org/28631.

Seeff, Leonard B. “The History of the ‘Natural History’ of Hepatitis C(1968–2009).” *Liver International : Official Journal of the International Association for the Study of the Liver* 29, no. 0 1 (January 2009): 89–99. https://doi.org/10.1111/j.1478-3231.2008.01927.x.

Seley-Radtke, Katherine L., and Mary K. Yates. “The Evolution of Nucleoside Analogue Antivirals: A Review for Chemists and Non-Chemists. Part 1: Early Structural Modifications to the Nucleoside Scaffold.” *Antiviral Research* 154 (June 2018): 66–86. https://doi.org/10.1016/j.antiviral.2018.04.004.

Chuck Grassley: Unted States Senator For Iowa. “Senators Seek Details on Sovaldi Pricing | Chuck Grassley,” July 11, 2014. https://www.grassley.senate.gov/news/news-releases/senators-seek-details-sovaldi-pricing.

Shadlen, Kenneth C., Bhaven N. Sampat, and Amy Kapczynski. “Patents, Trade and Medicines: Past, Present and Future.” *Review of International Political Economy* 27, no. 1 (January 2, 2020): 75–97. https://doi.org/10.1080/09692290.2019.1624295.

Sharma, Satyavan, and Nitya Anand. “Chapter 4 - Organometaliics.” In *Pharmacochemistry Library*, edited by Satyavan Sharma and Nitya Anand, 25:124–47. Approaches to Design and Synthesis of Antiparasitic Drugs. Elsevier, 1997. https://doi.org/10.1016/S0165-7208(97)80026-8.

Shepardson, David. “GM, Philips to Supply 73,000 U.S. Ventilators in $1.1 Billion Effort.” *Reuters*, April 8, 2020. https://www.reuters.com/article/us-health-coronavirus-gm-idUSKBN21Q1YA.

Shi, Leiyu, and Douglas A. Singh. *Essentials of the U. S. Health Care System*. Jones & Bartlett Publishers, 2009.

Shiel, William. “Definition of Nucleocapsid.” Accessed July 24, 2019. https://www.medicinenet.com/script/main/art.asp?articlekey=24449.

Shilts, Randy. *And the Band Played on : Politics, People, and the AIDS Epidemic*. New York: St. Martin’s Press, 1987.

Shorman, Jonathan. “591 Kansas Inmates Have Hepatitis C. It Would Cost about $9 Million to Treat Them All.” *Kansas City Star*, February 20, 2019. https://www.kansascity.com/news/politics-government/article226528715.html.

Silverman, Ed. “Gilead Patent for Its Hepatitis C Drug Is Invalidated by Chinese Authorities.” *STATNews*, August 13, 2018. https://www.statnews.com/pharmalot/2018/08/13/gilead-patents-hepatitis-china/.

———. “HHS Sues Gilead for Refusing to Do Licensing Deal on HIV Prevention Pills.” *STAT*, November 7, 2019. https://www.statnews.com/pharmalot/2019/11/07/hhs-gilead-hiv-prevention-patents-lawsuit/.

———. “How Illinois Allocates $84,000 Drug for Hepatitis C.” *Wall Street Journal*, August 4, 2014, sec. Business. http://www.wsj.com/articles/how-illinois-allocates-84-000-drug-for-hepatitis-c-1407114940.

———. “The VA Got a Good Price for a Hep C Drug. Why Not Medicare?” *STAT*, March 7, 2017. https://www.statnews.com/pharmalot/2017/03/07/veternas-hepatitis-c-drug-prices/.

———. “U.K. Reaches ‘first-of-Its-Kind’ Deal with Drug Makers for Hepatitis C - STAT.” *STAT News*, April 30, 2019. https://www.statnews.com/pharmalot/2019/04/30/uk-hepatitis-drug-prices/.

Simmonds, Peter, Paul Becher, Jens Bukh, Ernest A Gould, Gregor Meyers, Tom Monath, Scott Muerhoff, et al. “ICTV Virus Taxonomy Profile: Flaviviridae.” *The*

Journal of General Virology 98, no. 1 (January 2017): 2–3. https://doi.org/10.1099/jgv.0.000672.

Simmons-Duffin, Selena. "Louisiana's Novel 'Subscription' Model For Pricey Hepatitis C Drugs Gains Approval." *NPR*, June 26, 2019. https://www.npr.org/sections/health-shots/2019/06/26/736312262/louisianas-novel-subscription-model-for-pricey-hepatitis-c-drugs-gains-approval.

Smith, Alex. "Locked Up And Untreated: One Missouri Inmate's Quest For Hepatitis C Treatment," May 9, 2018. https://news.stlpublicradio.org/post/locked-and-untreated-one-missouri-inmate-s-quest-hepatitis-c-treatment.

———. "Missouri Faces Costly Dilemma: How To Treat Inmates With Hepatitis C?" *NPR.Org*, January 19, 2018. https://www.npr.org/sections/health-shots/2018/01/19/578425032/missouri-faces-costly-dilemma-how-to-treat-inmates-with-hepatitis-c.

Spector, Mike, Jessica DiNapoli, and Nate Raymond. "Exclusive: OxyContin Maker Purdue Pharma Exploring Bankruptcy -Sources." *Reuters*, March 5, 2019. https://www.reuters.com/article/uk-purduepharma-bankruptcy-exclusive-idUSKCN1QL1KP.

Staley, Eddie. "Pharmasset Announces Intent to Amend QUANTUM Trial." *Business Insights: Global*, January 16, 2011. http://bi.galegroup.com.ezproxy1.lib.asu.edu/global/article/GALE%7CA275049166/adc42e0c1e4f179cb9d2482d538a82f3?u=asuniv.

Stevens, Ashley J. "The Enactment of Bayh–Dole." *The Journal of Technology Transfer* 29, no. 1 (January 2004): 93–99. https://doi.org/10.1023/B:JOTT.0000011183.40867.52.

Strader, Doris B., and Leonard B. Seeff. "A Brief History of the Treatment of Viral Hepatitis C." *Clinical Liver Disease* 1, no. 1 (February 1, 2012): 6–11. https://doi.org/10.1002/cld.1.

Strickland, G. Thomas. "Liver Disease in Egypt: Hepatitis C Superseded Schistosomiasis as a Result of Iatrogenic and Biological Factors." *Hepatology (Baltimore, Md.)* 43, no. 5 (May 2006): 915–22. https://doi.org/10.1002/hep.21173.

Strickler, Laura. "Purdue Pharma Offers $10-12 Billion to Settle Opioid Claims." *NBC News*, August 27, 2019. https://www.nbcnews.com/news/us-news/purdue-pharma-offers-10-12-billion-settle-opioid-claims-n1046526.

Subcommittee on National Security Veterans Affairs and International Relations of the Committee on Government Reform. HEPATITIS C: ACCESS, TESTING, AND TREATMENT IN THE VA HEALTH CARE SYSTEM, § Subcommittee on National

Security Veterans Affairs and International Relations of the Committee on Government Reform (2000). https://www.gpo.gov/fdsys/pkg/CHRG-106hhrg73167/pdf/CHRG-106hhrg73167.pdf.

Swan, Tracy., and HIV/AIDS Bureau. *Care and Treatment for Hepatitis C and HIV Coinfection: Expanding Access Though the Ryan White CARE Act*. Washington, D.C., UNITED STATES: United States Department of Health and Human Services, 2006. http://purl.access.gpo.gov/GPO/LPS77545.

Tan, Siang Yong, and Yvonne Tatsumura. "Alexander Fleming (1881–1955): Discoverer of Penicillin." *Singapore Medical Journal* 56, no. 7 (July 2015): 366–67. https://doi.org/10.11622/smedj.2015105.

Taylor, Jessamyn. "Caring for Ryan White": The Fundamentals of HIV/AIDS Treatment Policy," 2005.

The Editors of Encyclopaedia Britannica. "Antibody | Definition, Structure, Function, & Types." In *Encyclopedia Britannica*. Accessed August 28, 2020. https://www.britannica.com/science/antibody.

The Price of Solvaldi and its Impact on the United States Health Care System, § COMMITTEE ON FINANCE UNITED STATES SENATE (2015).

The Henry J. Kaiser Family Foundation| HIV/AIDS. "The Ryan White HIV/AIDS Program: The Basics," February 4, 2019. https://www.kff.org/hivaids/fact-sheet/the-ryan-white-hivaids-program-the-basics/.

Thornton, K., P. Deming, M. Sedillo, and S. Arora. "FRI-186 - Treatment of Chronic Hepatitis C Virus (HCV) Infections with Direct Acting Antivirals in the New Mexico State Prison System Using the Project ECHO Model." *Journal of Hepatology*, Abstracts of The International Liver Congress 2017 — 52nd Annual meeting of the European Association for the Study of the Liver, 66, no. 1, Supplement (January 1, 2017): S492. https://doi.org/10.1016/S0168-8278(17)31380-6.

Tong, Yimin, Dimitri Lavillette, Qingchao Li, and Jin Zhong. "Role of Hepatitis C Virus Envelope Glycoprotein E1 in Virus Entry and Assembly." *Frontiers in Immunology* 9 (June 19, 2018). https://doi.org/10.3389/fimmu.2018.01411.

Trooskin, Stacey B., Helen Reynolds, and Jay R. Kostman. "Access to Costly New Hepatitis C Drugs: Medicine, Money, and Advocacy." *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 61, no. 12 (December 15, 2015): 1825–30. https://doi.org/10.1093/cid/civ677.

Tucker, Miriam. "Costs for Hepatitis C Treatment Skyrocket." *Medscape*, November 3, 2013. http://www.medscape.com/viewarticle/814295.

Turner, Ashley. “Drugmaker Insys Shares Tank after Saying Opioid Lawsuits May Force It into Bankruptcy.” *CNBC*, May 13, 2019. https://www.cnbc.com/2019/05/13/insys-stock-tanks-after-saying-it-may-be-forced-to-file-bankruptcy.html.

United States Department of Agriculture. “Penicillin: Opening the Era of Antibiotics : USDA ARS.” Accessed January 3, 2020. https://www.ars.usda.gov/midwest-area/peoria-il/national-center-for-agricultural-utilization-research/docs/penicillin-opening-the-era-of-antibiotics/.

Patent Docs. “United States v. Gilead Sciences, Inc.” Accessed February 4, 2020. https://www.patentdocs.org/2019/12/united-states-v-gilead-sciences-inc.html.

United States Senate. “U.S. Senate: A History of Notable Senate Investigations.” Accessed March 27, 2019. https://www.senate.gov/artandhistory/history/common/briefing/Investigations.htm#2.

U.S.C. Title 28 Sec. 1498, 28 U.S.C § 1498 (1910). https://www.govinfo.gov/content/pkg/USCODE-2011-title28/html/USCODE-2011-title28-partIV-chap91-sec1498.htm.

Verma, Sonia, Rajnikant Dixit, and Kailash C. Pandey. “Cysteine Proteases: Modes of Activation and Future Prospects as Pharmacological Targets.” *Frontiers in Pharmacology* 7 (April 25, 2016). https://doi.org/10.3389/fphar.2016.00107.

Vertex Pharmaceuticals Incorporated. “FDA Approves INCIVEK™ (Telaprevir) for People with Hepatitis C.” Vertex Pharmaceuticals, May 23, 2011. https://investors.vrtx.com/news-releases/news-release-details/fda-approves-incivektm-telaprevir-people-hepatitis-c.

Veterans Healthcare Administration. “About VHA - Veterans Health Administration.” General Information. Accessed September 2, 2019. https://www.va.gov/health/aboutvha.asp.

Wagner, Judith L., and Elizabeth McCarthy. “International Differences in Drug Prices.” *Annual Review of Public Health* 25, no. 1 (2004): 475–95. https://doi.org/10.1146/annurev.publhealth.25.101802.123042.

Wan, William, and Moriah Balingit. “WHO Warns Young People Are Emerging as Main Spreaders of the Coronavirus.” *Washington Post*. Accessed August 28, 2020. https://www.washingtonpost.com/health/who-warns-young-people-are-emerging-as-main-spreaders-of-the-coronavirus/2020/08/18/1822ee92-e18f-11ea-b69b-64f7b0477ed4_story.html.

Wang, Kai, Shiqi Xie, and Bing Sun. “Viral Proteins Function as Ion Channels.” *Biochimica et Biophysica Acta (BBA) - Biomembranes*, Viral Ion Channels, 1808, no. 2 (February 1, 2011): 510–15. https://doi.org/10.1016/j.bbamem.2010.05.006.

Watanabe, Kyoichi A., and Balakrishna S. Pai. 3’-or 2’-hydroxymethyl substituted nucleoside derivatives for treatment of hepatitis virus infections. World Intellectual Property Organization WO2001079246A2, filed April 13, 2001, and issued October 25, 2001. https://patents.google.com/patent/WO2001079246A2/en.

Weiczner, Jen. “Gilead CEO John Martin Is Stepping Down After 20 Years.” *Fortune*. Accessed February 4, 2020. https://fortune.com/2016/01/29/gilead-ceo-john-martin/.

Williams, Corinne L. “Ralf Bartenschlager, Charles Rice, and Michael Sofia Are Honored with the 2016 Lasker~DeBakey Clinical Medical Research Award.” *The Journal of Clinical Investigation* 126, no. 10 (October 3, 2016): 3639–44. https://doi.org/10.1172/JCI90179.

World Health Organization. “Global Hepatitis Report, 2017.” World Health Organization, 2017. http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1.

———. “Global Report on Access to Hepatitis c Treatment: Focus on Overcoming Barriers.” Geneva Switzerland: World Health Organization, October 2016. http://apps.who.int/iris/bitstream/10665/250625/1/WHO-HIV-2016.20-eng.pdf?ua=1.

———. “Progress Report on Access to Hepatitis C Treatment: Focus on Overcoming Barriers in Low- and Middle-Income Countries.” World Health Organization, 2018.

———. “WHO | Egypt: 35 Million People Receive Hepatitis C Test.” WHO, March 30, 2019. http://www.who.int/hepatitis/news-events/egypt-hepatitis-c-testing/en/.

———. “WHO | Yellow Fever Outbreak Angola, Democratic Republic of the Congo and Uganda 2016-2017.” WHO, February 14, 2017. http://www.who.int/emergencies/yellow-fever/en/.

———. “WHO EMRO | Egypt Launches National Communication Campaign on Hepatitis C | Egypt-Events | Egypt.” Accessed February 3, 2020. http://www.emro.who.int/egy/egypt-events/hepatitis-c-campaign.html.

World Trade Organization. “WTO | Intellectual Property (TRIPS) - TRIPS and Public Health.” World Trade Organization. Accessed January 28, 2020. https://www.wto.org/english/tratop_e/trips_e/pharmpatent_e.htm.

———. “WTO | Understanding the WTO - Intellectual Property: Protection and Enforcement.” World Trade Organization. Accessed January 28, 2020. https://www.wto.org/english/thewto_e/whatis_e/tif_e/agrm7_e.htm.

Ron Wyden: United States Senator for Oregon. “Wyden-Grassley Sovaldi Investigation Finds Revenue-Driven Pricing Strategy Behind $84,000 Hepatitis Drug | U.S. Senator Ron Wyden of Oregon,” December 1, 2015. https://www.wyden.senate.gov/news/press-releases/wyden-grassley-sovaldi-investigation-finds-revenue-driven-pricing-strategy-behind-84000-hepatitis-drug.

Yin, Xueqiang. “Mechanism Based Design and Synthesis of Nucleoside Analogues as Antiviral Agents.” Ph.D., Auburn University, 2002. http://search.proquest.com/docview/304800333/abstract/5D8AAF60D73A4F9FPQ/1.

Zamor, Riche. “Measuring the Value of Your Product.” Phase2, April 16, 2017. https://www.phase2technology.com/blog/measuring-value-your.

APPENDIX A

FEDERAL FUNDING OF RESEARCHERS FOR HEPATITIS C TREATMENTS

Researcher Name	NIH Grant Number(s) Year granted in parentheses	Grant Name	Grant Substance	Resulting publications	Institution
Jinfa Du	AI056794 01 (2003)	DIOXOLANE NUCLEOSIDES AS ANTIVIRAL AGENTS	(-)-beta-D-5-fluoro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine	N4-hydroxycytosine dioxolane nucleosides and their activity against hepatitis B virus Synthesis of 5'-C-methyl-1',3'-dioxolan-4'-yl nucleosides	Pharmasset, INC
Jinfa Du	DK066922 01 - 03 (2004 – 2006)	2'-AND/OR4'-C-MODIFIED NUCLEOSIDES AS ANTIHCV AGENTS	2'-C- and/or 4'-C-modified nucleosides, as well as 3'-deoxynucleosides	Synthesis of beta-enantiomers of N4-hydroxy-3'-deoxypyrimidine nucleosides and their evaluation against bovine viral diarrhoea virus and hepatitis C virus in cell culture	Pharmasset
Nigel Bourne	AIO57156 05S1 - 06 (2008 – 2009),	IDENTIFICATION AND CHARACTERIZATION OF NOVEL FLAVIVIRUS ANTIVIRALS	Screening process for antivirals	List of publications, Nigel Bourne not listed as author on any; largely unrelated viruses	UNIVERSITY OF TEXAS MED BR GALVESTON

Nigel Bourne	DK06770601 (2004)	MORPHOLINO ANTISENSE DRUGS FOR HEPATITIS C VIRUS	Antisense PMO oligomers	None	AVI BIOPHARMA, INC
John D. Morrey	N01AI50036-4-0-0 2—5 (2007)	ANIMAL MODELS FOR THE PREVENTION AND TREATMENT OF HEPATITIS B AND HEPATITIS C	Examination of animal models	No publication information available	No information available
Raymond F. Schinazi	N01AI005078-000 - 011(1990 – 1994)	IN VITRO TEST SYSTEMS FOR COMBINED CHEMOTHERAPIES	2',3'-dideoxy-3'-thiacytidine (BCH-189)	Activities of the four optical isomers of 2',3'-dideoxy-3'-thiacytidine (BCH-189) against human immunodeficiency virus type 1 in human lymphocytes	Emory University
Raymond F. Schinazi	N01AI005078-000 – 002	IN VITRO TEST SYSTEMS FOR COMBINED CHEMOTHERAPIES AGAINS	2',3'-dideoxy-3'-thiacytidine (BCH-189)	Activities of the four optical isomers of 2',3'-dideoxy-3'-thiacytidine (BCH-189) against human immunodeficiency virus type 1 in human lymphocytes	Emory University
Raymond F. Schinazi	R01 AI041980-01 – 09 (1997 – 2005)	NUCLEOSIDES WITH DUAL ANTIHIV AND HBV ACTIVITY	d- and l-2′,3′-Didehydro-2′,3′-Dideoxy-	Full NIH list of related publications exceeds ten publications:	Emory University

			3′-Fluoro-Carbocyclic Nucleosides	Link To Full List	
Raymond F. Schinazi	R01 CA053892-01 – 05 (1991 – 1995)	BORON-CONTAINING NUCLEOSIDES FOR NEUTRON CAPTURE THERAPY	beta-5-o-carboranyl-2'-deoxyuridine	Cellular pharmacology of the D- and L-enantiomers of beta-5-o-carboranyl-2'-deoxyuridine Synthesis and biological properties of the four optical isomers of 5-o-carboranyl-2',3'-didehydro-2',3'-dideoxyuridine Carboranyl oligonucleotides. 3. Biochemical properties of oligonucleotides containing 5-(o-carboranyl-1-yl)-2'-deoxyuridine Pharmacokinetics of 5-carboranyl-2'-deoxyuridine in rats Synthesis and biological	

				properties of 5-o-carboranyl-1-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl)uracil Cellular pharmacology and biological activity of 5-carboranyl-2'-deoxyuridine Phenylselenenyl- and phenylthio-substituted pyrimidines as inhibitors of dihydrouracil dehydrogenase and uridine phosphorylase Patents: Nucleosides and oligonucleotides containing boron clusters Treatment of urogenital cancer with boron neutron capture therapy	
Raymond F. Schinazi	R01 CA043255 01 - 03	BORON-CONTAINING NUCLEOSIDES FOR	adenosine deaminase	None	Emory University

		NEUTRON CAPTURE THERAPY	deoxyuridine		
David N. Frick	AI05239501 A1 - 05 (2003 -2007)	Enzymatic differences among HCV genotypes	NS3 Helicase and NS5B polymerase	Full NIH list of related publications exceeds ten publications: Link to Full List	University of Wisconsin Milwaukee
David N. Frick	AI088001 01 -02 (2008 - 2010)	Antiviral potential of Helicase inhibitors	Collection of helicase inhibitors	Full NIH list of related publications exceeds ten publications: Link to Full List	University of Wisconsin Milwaukee
Julie A. Heck	1F23DK0832 3701A2 - 03 (2008-2010)	MOLECULAR MECHANISM OF CELLULAR ACTIVATION OF THE HCV POLYMERASE	cyclophilin B (A factor in activity of NS5B and potential target)	None	New York Medical College
Michael Sofia	R43 AI037399 01A1 (1995)	NOVEL ANTISENSE DNA CONJUGATES AS ANTIHIV AGENTS	N/A	None	Transcell Technologies, INC
Krzysztof W. Pankiewicz	1R43AI05672 0-01 (2003)	NOVEL CLASS OF COMPOUNDS FOR TREATMENT OF HCV INFECTIONS	3-beta-D-ribofuranosyl-9,5'-cyclopurine	Synthesis and biological activity of 5',9-anhydro-3-purine-isonucleosides as potential anti-hepatitis C virus agents Synthesis and structure-activity relationships of	Pharmasset, INC

				novel anti-hepatitis C agents: N3,5'-cyclo-4-(beta-D-ribofuranosyl)-vic-triazolo[4,5-b]pyridin-5-one derivatives. Synthesis of N3,5'-cyclo-4-(beta-D-ribofuranosyl)-vic-triazolo[4,5-b]pyridin-5-one and its 3'-deoxysugar analogue as potential anti-hepatitis C virus agents Synthesis and anti-hepatitis C virus activity of nucleoside derivatives of N3, 5'-anhydro-4-(beta-D-ribofuranosyl)-8-aza-purin-2-ones Synthesis and anti-HCV activity of N9,5'-cyclo-3-(beta-D-ribofuranosyl)-	

				8-azapurin-2-one derivatives Synthesis of N3,5'-cyclo-4-(beta-D-ribofuranosyl)-vic-triazolo[4,5-b]pyridin-5-one, a novel compound with anti-hepatitis C virus activity	
Lieven J. Stuyver	1R43AI052686-01 (2002)	MODIFIED NUCLEOSIDES FOR HEPATITIS C VIRUS	'-deoxy-2'-fluorocytidine D-N4-hydroxycytidine	Metabolism of the anti-hepatitis C virus nucleoside beta-D-N4-hydroxycytidine in different liver cells. Inhibition of the subgenomic hepatitis C virus replicon in huh-7 cells by 2'-deoxy-2'-fluorocytidine. Dynamics of subgenomic hepatitis C virus replicon RNA levels in Huh-7 cells after exposure to nucleoside antimetabolites.	Pharmasset INC