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ISSUE BRIEF

Hepatitis C and Drug Pricing: The Need for a Better Balance

Hepatitis C virus (HCV) is transmitted by contact with the blood of a person living with HCV. HCV can be transmitted through multiple routes, including needle sharing, unsterilized medical equipment, contaminated blood products, sexual contact, and perinatally.[1]

Globally, approximately 185 million people are living with HCV. The majority of individuals who have HCV are unaware of their status. While most new HCV infections never result in significant disease, some 15–30% of chronic HCV cases will result in cirrhosis of the liver and 5–7% will result in liver failure.[2] Untreated individuals may also develop advanced liver fibrosis and hepatocellular carcinoma (liver cancer).[3] Approximately 350,000 people across the globe die every year from liver complications associated with HCV.[4]

HCV has six circulating genotypes (numbered 1 through 6) along with various subtypes. Global prevalence, treatment options, and treatment success rates for each genotype vary considerably. Genotype 1 is the most prevalent in the United States.

In this brief, we review drug pricing for new hepatitis C medications and pose basic questions of fairness and medical ethics. Although we focus on Gilead and its hepatitis C drug sofosbuvir (marketed as Sovaldi®), the issues we highlight are broadly applicable to other manufacturers of hepatitis C medications.

Summary

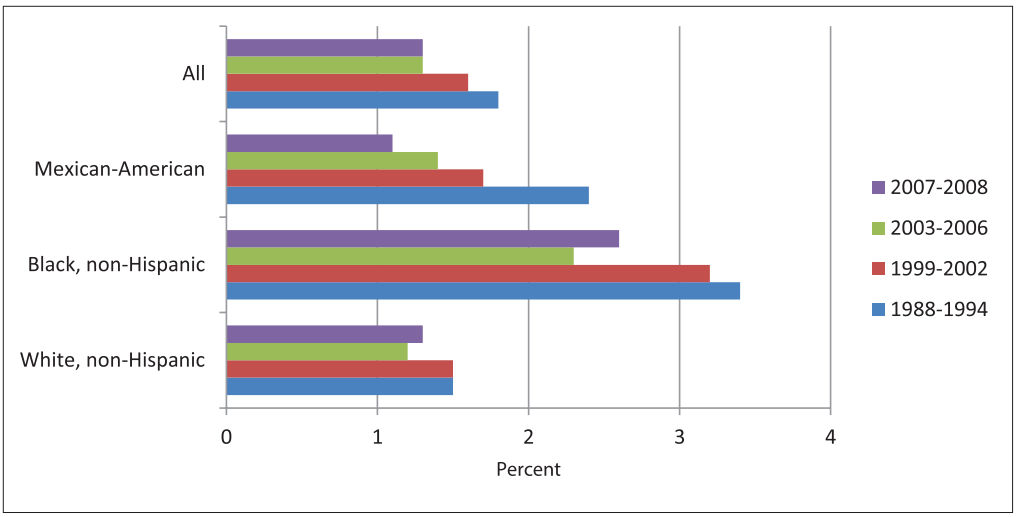
- **Background:** New pharmaceutical breakthroughs have made curing hepatitis C (HCV) infection easier and more effective.
- **The Issue:** These new drugs have been priced at aggressively high rates that bear no relation to the cost of research and development. With as many as 185 million people living with HCV globally, including three million Americans, this aggressive drug pricing will place an unjustifiable and unsustainable burden on domestic and global health system budgets.
- **amfAR's View:** Despite important price reductions for low- and middle-income countries, the astronomical prices demanded by Gilead and AbbVie for their HCV treatments will inevitably limit access to the drugs, leading to unnecessary loss of life.

Impact of Hepatitis C in the United States

Roughly 3.2 million Americans have chronic HCV infection[5] and approximately 12,000 Americans die every year from chronic liver disease associated with the virus.[6] Those at greatest risk for HCV include recipients of blood transfusions and organ donations prior to 1992,[7] people with hemophilia, hemodialysis patients, people living with HIV, and people who inject drugs.[8,7] HCV infections in the United States declined steadily from 1982 to 2010, averaging approximately 200,000 infections per year from 1982 to 1991, 43,600 per year from 1992 to 2001, and 19,100 per year from 2002 to 2010.[10] However, there has been a 75% increase in reported cases from 2010 to 2012.[11]

The burden of HCV in the U.S. is disproportionately borne by racial and sexual minority populations. HCV prevalence among African-Americans and some Latino communities (Mexican-Americans) is consistently higher than among white Americans, with an HCV rate among African-Americans almost double that of the general population. And infection rates among gay and bisexual men in the U.S. have steadily increased in the past decade, particularly among those living with HIV.[12]

Figure 1. HCV Prevalence Among Persons Six Years and Older in the United States for Select Years by Race/Ethnicity



Source: McQuillan GM, Kruszon-Moran D, Denniston MM, and Hirsch R. Centers for Disease Control and Prevention. National Center for Health Statistics Data Brief. Viral Hepatitis*. March 2010. http://www.cdc.gov/nchs/data/databriefs/db27.pdf*

A Costly Cure for Hepatitis C

Historically, HCV treatment has been lengthy and of uncertain effectiveness. Standard treatment regimens required 24–48 weeks and cure rates ranged from 50% to 80% of cases. Since late 2013, new direct-acting antiviral (DAA) drugs have been approved for the treatment of HCV by the U.S. Food and Drug Administration (FDA). These new treatment regimens (in combination with older HCV drugs) have reduced treatment duration to 12–24 weeks, decreased side effects, and improved outcomes, with cure rates of 85–95% across all patient populations.

The FDA has approved four new HCV treatment regimens since late 2013 (Table 1). While the new medications are welcome advances, they come with a hefty price tag. For example, sofosbuvir has been priced in the United States at $84,000 for a 12-week course of treatment. Such exorbitant price setting has once again brought the issue of drug pricing to the fore in the U.S. and around the world.

Implications of new HCV medications: a burden on U.S. health systems

The costs associated with the wave of new treatments for HCV have generated controversy. Most of the criticism to date has been directed toward Gilead over the pricing of sofosbuvir at approximately $1,000 per pill.[22] Gilead, however, is not alone in this regard, as AbbVie's recently approved Viekira Pak

Table 1. HCV Treatment Regimens Since 2013

Active Ingredient	Brand Name	Treatment Formulation	Genotype Approval	Treatment Duration	Pharmaceutical Company	List Price*	Total Regimen Cost*
simeprevir[13]	Olysio	simeprevir + peginterferon alfa + ribavirin	1	12 weeks (simeprevir) 24–48 weeks (total)	Medivir & Janssen Pharmaceutical	$66,360	$85,960[14]
sofosbuvir[15]	Sovaldi	sofosbuvir + pegylated interferon + ribavirin	1, 4	12 weeks	Gilead Sciences	$84,000	$103,600[16]
		sofosbuvir + ribavirin	2	12 weeks		$84,000	$85,100[17]
		sofosbuvir + ribavirin	3	24 weeks		$168,000	$169,100[18]
ledipasvir/ sofosbuvir[19]	Harvoni	ledipasvir + sofosbuvir	1	12 weeks	Gilead Sciences	$94,500	$94,500
ombitasvir/ paritaprevir/ ritonavir[20]	Viekira Pak	ombitasivir + paritaprevir + ritonavir + dasabuvir	1	12–24 weeks	AbbVie Inc.	$83,319	$83,319

** The prices here do not consider all possible prescribed regimens but are indicative of the total list price for a treatment regimen. List prices for all drugs sourced from University of Washington, Hepatitis C Online project.[21]*

Even accounting for all available discounts, treating all HCV-infected individuals in the United States would cost approximately $110 billion.

(ombitasvir, paritaprevir and ritonavir) has only slightly undercut Gilead,[23] and the overall cost of a treatment regimen with Janssen's simeprevir is approximately $85,000.

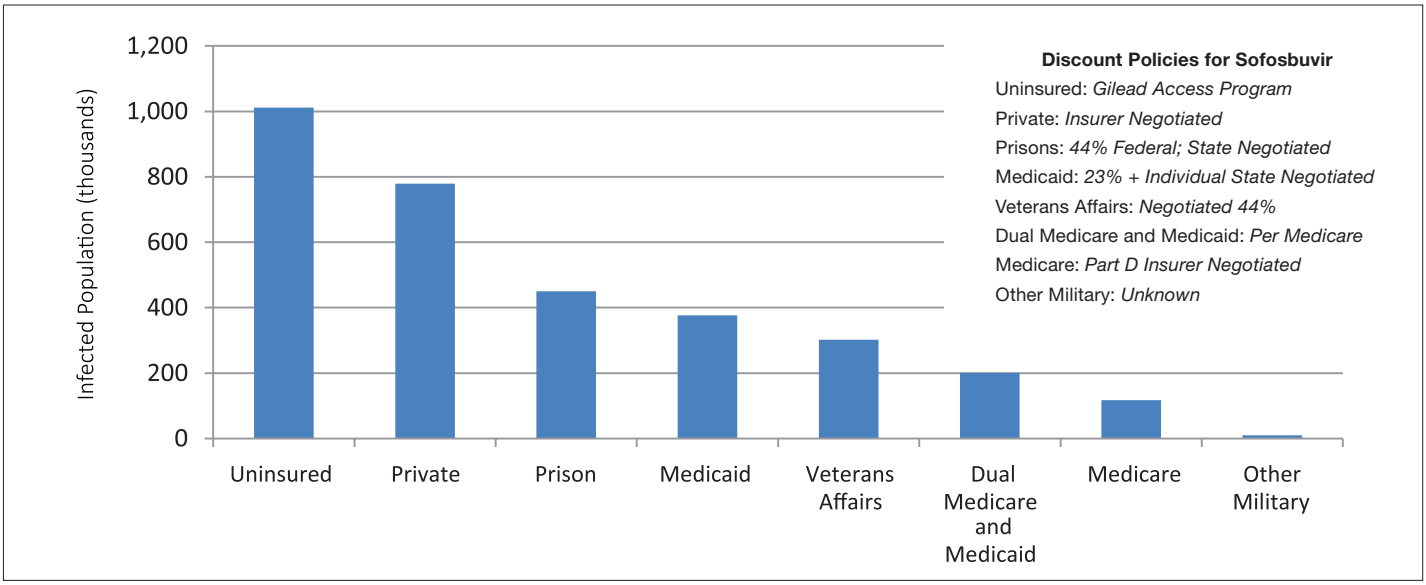
Using just list prices, one estimate found that treating all HCV-infected individuals in the U.S. with sofosbuvir would cost more than $268 billion.[24] However, virtually all providers get some sort of discount off the list price (Figure 2). But even taking these into account, the cost of treating all HCV-infected individuals in the U.S. would still be approximately $110 billion, a figure completely unrelated to the cost of developing the drug.[25]

Controversial pricing of HCV medication has led to outcries from virtually all corners of the U.S. Senators Ron Wyden and Chuck Grassley from the Senate Finance Committee have written to Gilead requesting the evidence and basis to support their pricing.[26] House Committee on Energy and Commerce members Frank Pallone, Jr., Diana DeGette and Henry Waxman (retired, 2014) have requested a similar briefing from Gilead.[27] State Medicaid directors have also written to both Senate and House committees about the difficulty states have experienced in securing steeper discounts from Gilead, and the unsustainable effect the price of sofosbuvir is having on state Medicaid budgets.[28]

It is estimated that as many as one million Americans with hepatitis C are at 'highest' or 'high' priority for immediate treatment based upon established medical guidelines.[29] Many Americans with hepatitis C are uninsured, but the majority have access to some form of insurance, either through public government programs or private coverage. However, the new HCV drugs will still be out of reach for many insured individuals who are clinically eligible for treatment because payers are limiting access to these costly regimens:

- **Medicaid**: By law, Medicaid is required to provide access to all FDA-approved outpatient drugs so long as the manufacturer provides a minimum 23% rebate.[30] However, the price of new hepatitis C drugs has prompted cost-saving measures by Medicaid, such as the creation of numerous hurdles that patients must overcome before they can access treatment. In Illinois, patients are required to meet 25 different criteria before they may be prescribed sofosbuvir.[31] Other states, such as Arizona, have imposed a once-in-a-lifetime rule that denies patients who have previously received treatment with sofosbuvir any further coverage for the drug in the event they become infected again.[32] Molina Healthcare, which operates Medicaid managed-care plans for 11 states, has told state officials that it would not be able to afford covering the drug.[33]
- **Medicare**: Medicare is also greatly affected by the cost of sofosbuvir. According to one estimate, if only 7% of HCV-infected Medicare Part D enrollees were treated with sofosbuvir, Medicare spending would increase by $2 billion in new Part D drug costs in 2015 over 2014.[34] This would

Figure 2. HCV Burden by Insurance Type and Associated Discount Policy, U.S.



Source: Epidemiology data; Milliman, Inc., NY. Health Care Reform and Hepatitis C: A Convergence of Risk and Opportunity. *December 10, 2013. http://us.milliman.com/uploadedFiles/insight/2013/convergence-of-risk-and-opportunity.pdf. Discount data; per citations in text.*

represent a 3% increase in federal Part D outlays and Part D premiums due to sofosbuvir alone.[35] If 21% were treated, Medicare spending would increase by $6.5 billion in new Part D drug costs in 2015 over 2014.[36] This, in turn, would represent an 8% increase in federal Part D outlays and Part D premiums.[37]

It is important to keep in mind that these estimates are conservative—they represent only the cost increase due to sofosbuvir, and do not account for the increased cost due to other medications that are often prescribed alongside sofosbuvir, or the laboratory and medical costs involved in delivering treatment.[38] Although these figures also do not discount savings Medicare will experience from reduced numbers of hospitalizations and liver transplants associated with HCV infection, the current price of HCV treatment remains prohibitively high and out of reach for many, even when such discounts are applied.

If only 7% of HCV-infected Medicare Part D enrollees were treated with sofosbuvir, Medicare spending would increase by $2 billion in new Part D drug costs in 2015 over 2014.[1] **This would represent a 3% increase in federal Part D outlays and Part D premiums, due to sofosbuvir alone.**

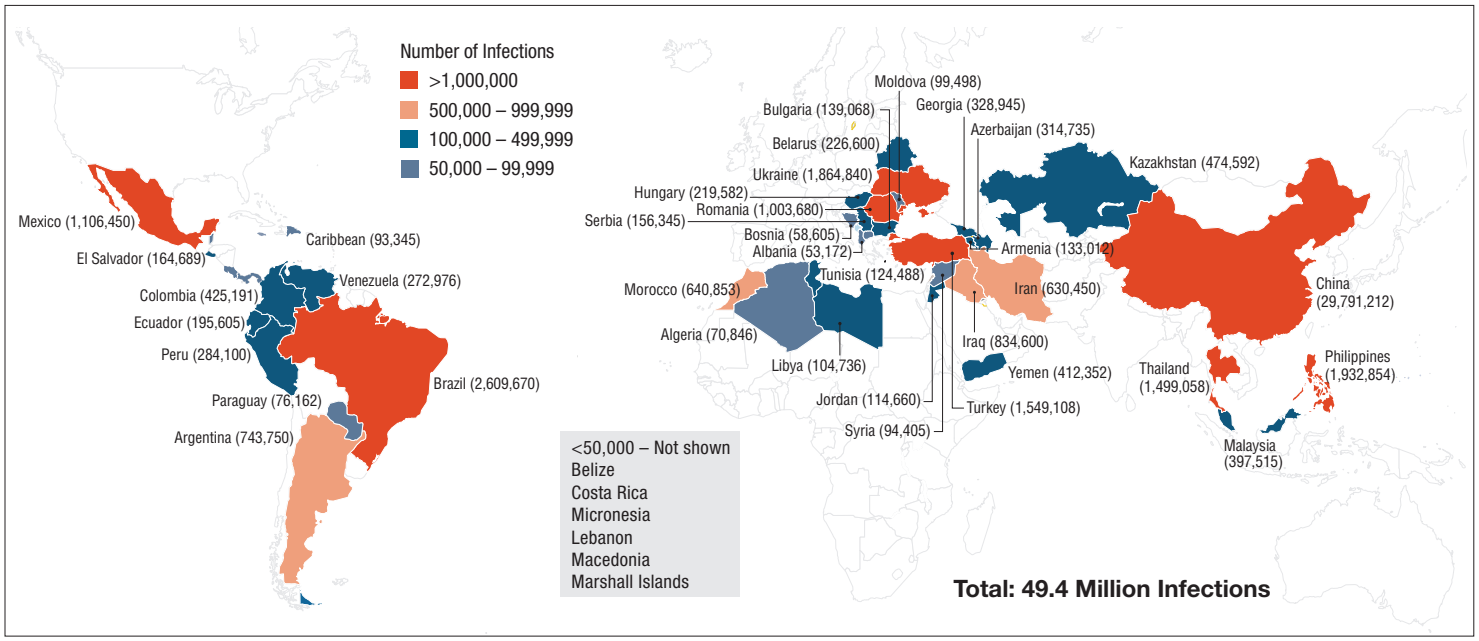
- **Federal prison system**: Current Federal Bureau of Prisons (BOP) guidance for treatment of HCV recommends treatment with sofosbuvir for all genotypes for inmates with advanced disease or HIV co-infection.[39] While the BOP has secured a 44% discount from Gilead,[40] the cost implications for the prison system and taxpayers are still prohibitive. The CDC estimates that 12–35% of prison inmates have chronic HCV infection.[41] Even if only one-third of those with chronic HCV infection in Federal prisons require treatment per BOP guidelines, it could push the per inmate cost of incarceration up between 6% and 19%.[42]
- **State prison systems**: For state prison systems, medication discounts must be negotiated individually at the state level. Without discounts, the per inmate cost of state prison systems could be pushed up 12–34%, depending on the prevalence of HCV among inmates.[43] This has enormous budgetary implications for states, and most prisons are actively denying inmates access to sofosbuvir (and other similar HCV medications) unless individual cases become clinically urgent or there are compelling financial reasons to provide the treatment, such as avoiding the high cost of a liver transplant for inmates with lengthy prison sentences.[44]
- **Private insurers**: For private insurers, the introduction of AbbVie's Viekira Pak has initiated a flurry of price negotiations that are seemingly driving the price down while expanding access to more patients. Shortly after being approved for marketing, Express Scripts—the largest prescription drug benefit manager in the U.S.—made Viekira Pak the preferred pharmacy formulation over Sovaldi/Harvoni, presumably because AbbVie was willing to discount its product more than Gilead.[45] Conversely, Gilead has negotiated with several providers including CVS, Aetna, and Humana to exclusively offer Sovaldi/Harvoni unless a patient has a clinical indication for Viekira Pak.[46] Indications are now that the level of discounts insurers have been able to secure are more than double what they were in 2014. While these are positive movements in terms of the resulting price reductions for the healthcare system overall, they make patients further subject to the business arrangements of insurance providers over their own, or their physician's, preferred choice of medications.

The high cost of treating HCV globally

The global impact of HCV is staggering. The World Health Organization (WHO) estimates that as many as 185 million people are living with hepatitis C, with up to 350,000 deaths annualy due to HCV-related liver disease.[47] Given the prevalence of HCV worldwide, these new HCV medications could have a profound impact on global health. However, price reductions for some countries do not necessarily make these drugs affordable. For instance, while the cost of treatment with sofosbuvir is highest in the United States at $84,000, it is estimated that it will cost approximately $55,000–57,000[48] in the United Kingdom and Canada and $66,000–$68,000 in Germany.[49] Though they represent three of the wealthiest countries in the world,[50] sofosbuvir is still considered all but unaffordable by the national health systems in the U.K. and Canada, and it remains to be seen at what price and for how many patients the German government will approve covering the drug.[51]

At the same time, some countries will have access to dramatic price reductions. Through an agreement negotiated between Gilead and the Egyptian government, sofosbuvir will be priced

Figure 3. HCV Burden in Middle-Income Countries Excluded from Gilead's Voluntary License



Source: Lavanchy, D. Evolving epidemiology of hepatitis C virus, Clin Microbiol Infect *2011; 17: 107–115 (2011).*

in Egypt at $900 for a 12-week course.[52] Subsequently, Gilead extended this pricing to other countries including India and Brazil.[53] In September 2014, Gilead also signed a voluntary license agreement with seven pharmaceutical companies in India, allowing them to sell generic sofosbuvir formulations in 91 developing countries, with a 7% royalty going to Gilead.[54]

The significance of this voluntary license has yet to be seen as prices for the generic formulations have not been released and guidelines for laboratory monitoring of treatment in resource-constrained settings have yet to be developed. In addition, many developing countries continue to lack sufficient infrastructure or the trained healthcare workers necessary to implement broad HCV treatment programs; and it likewise remains unclear whether political leaders will be able to mobilize the resources necessary to develop such capacity. Thus, while an estimate of the cost of manufacturing generic sofosbuvir has suggested prices could be as low as $68–136 for a 12-week course of treatment,[55] a major obstacle to the availability of HCV treatment in developing countries covered by voluntary licenses may actually be programmatic. Other potential barriers, such as the anti-diversion mechanisms that are part of the voluntary license agreement and are meant to prevent the re-selling of sofosbuvir to wealthy countries, have yet to be made public and could severely hamper genuine access to generic sofosbuvir in low- and middle-income countries.[56]

Although voluntary licenses may reduce the cost of HCV medications in certain low-income countries, such medications may remain out of reach for those in middle-income countries not covered by the licenses. In particular, Gilead has not made clear the criteria it used to determine the geographic range of the agreement. The 91 countries included in the agreement account for all countries designated as low-income by the World Bank, 37 lower-middle-income, 17 upper-middle-income, and two high-income countries, but exclude 13 lower-middle-income and 38 upper-middle-income countries.

For countries left out of the agreement (Figure 3), the default rules established under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) are maintained. This means that Gilead retains the exclusive right to sell sofosbuvir in these countries without any generic competition. While few would argue that high-income countries should have been included, Gilead's rationale for including Equatorial Guinea, for example, while excluding countries such as El Salvador or the Philippines has not been explained. Excluded lower- and upper-middle-income countries are estimated to have more than 49 million people with chronic HCV,[57] including more than 29 million in China alone, but will be required to negotiate prices with Gilead directly rather than being able to rely on the open terms of the voluntary license.

It must be noted that the initial patent application for sofosbuvir was recently rejected by the Indian Patent Office.[58] The significance of the rejection is not yet clear as

another patent application relating to sofosbuvir in India is still pending[59] and Gilead has already indicated it will appeal the decision.[60] In other countries, patents on sofosbuvir may already have been granted or patent applications may still be pending in the local patent office barring any production or importation without Gilead's consent.

In a more ideal setting, Gilead would enable the generic licensees to manufacture for all countries, with varying royalty rates being established for each country or country group. Doing so would ensure that generic manufacturing was done at a scale that would drive production to the lowest possible price while enabling Gilead to maintain a transparent tiered pricing strategy across countries.

Discrepancies in HCV Medication Development vs. Pricing: Sofosbuvir

Public records from the U.S. Securities and Exchange Commission (SEC) provide clues to the costs associated with the development of sofosbuvir. Prior to being purchased by Gilead, sofosbuvir was initially developed by Pharmasset, Inc., a small pharmaceutical company dedicated primarily to HCV treatments with no drugs yet approved by the FDA and three drugs (including sofosbuvir) in clinical development.[61] Public data for Pharmasset are available from 2001 on, and they show that its total research and development budget between January 2001 and September 2011 amounted to $281 million.[62,63] Including operating expenses, Pharmasset's total operations only amounted to $373 million.

With this research and development budget, Pharmasset managed to move sofosbuvir through phase 1 and several phase 2 human clinical trials and initiate phase 3 clinical trials. This was in addition to developing other hepatitis B, hepatitis C, and HIV drug candidates, some of which had made it to phase 2 testing.[64] Pharmasset's revenues over this period were $59 million. In 2011, when Gilead purchased the company for more than $11 billion, it reported earnings of only $897,000.

Clinical trials are generally the most expensive aspect of drug development, and after acquiring Pharmasset, Gilead incurred the expense of conducting phase 3 trials, seeking marketing approval from the FDA, and conducting ongoing post-market trials (see Figure 4).[65] Nonetheless, Gilead would be hard-pressed to suggest that the research and development costs of the phase 3 trials, on top of the $373 million in operations costs at Pharmasset, could justify its pricing of sofosbuvir.

This disparity between the purchase price for Pharmasset and the company's revenues over the previous decade reveals that Gilead was consciously aware that it was purchasing a future revenue stream. Interim or complete phase 2 trial data were already available by November 2011 that showed strong efficacy and good safety data, and led Pharmasset to initiate the phase 3 trials necessary for FDA approval.[66] That Gilead was willing to spend $11 billion for Pharmasset attests to this fact, and also to the point that the purchase price of Pharmasset is irrelevant to the discussion on the appropriate pricing of medications in relation to their development costs, or else any price could be justified based on poor valuations of companies and accounting gimmicks.

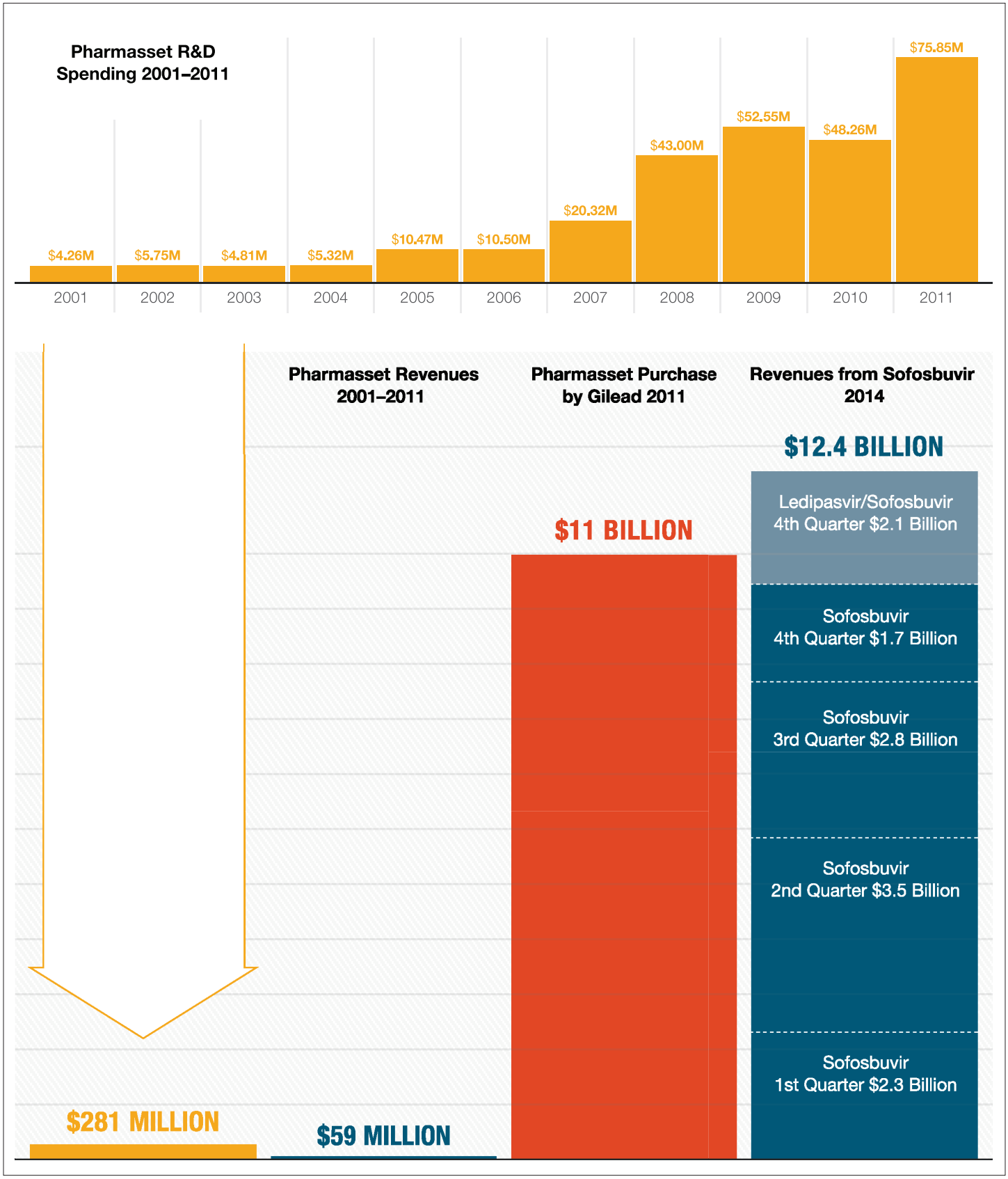
A Call for a Humane Balance Between Profit and Health

Intellectual property law is based on the principle that inventors, including large pharmaceutical companies, require protection from competition in order to incentivize investment in the products they create. The granting of a temporary monopoly is meant to encourage inventors to disclose their inventions and enter them into the market. In the case of pharmaceuticals, these protections have been combined with a policy environment in the U.S. in which pharmaceutical companies have the freedom to price their products, even at extremely disproportionate rates, without fear of government-imposed price controls. This contrasts with the practice in most other countries.[67]

Since its market debut, sofosbuvir alone has had sales revenue of $10.28 billion for Gilead. Including sales of Harvoni (ledipasvir/sofosbuvir), Gilead earned $12.41 billion from sofosbuvir in a single calendar year.

As this brief illustrates, we believe that Gilead should be criticized for the egregious pricing that impinges upon access in the U.S. and around the world. But this issue is bigger than one manufacturer and one health condition. Few pharmaceutical products are developed solely in the laboratories of for-profit corporations. Indeed, many drugs depend on basic research and other findings developed with taxpayer support to underpin or lay the foundations for advances brought to us by modern pharmaceutical

Figure 4. Gilead and Pharmasset: A Disproportionate Investment



manufacturers. When companies such as Gilead, Abbvie and others believe their primary responsibility is to their shareholders, there is a policy imbalance between public sector contributions to research and private sector reward. Therefore, broader structural changes are needed to alter the pricing incentives for manufacturers and not to allow the sky to be the limit for every new drug product, even ones that are as exciting and effective as new hepatitis C treatments.

In the case of sofosbuvir, the manner in which Gilead has both priced the drug and resisted calls for deep discounts to public payors and volume purchasers is legal, but the impact on people who need access to care and the programs that support them is unsustainable and unethical. Since its market debut, Sovaldi alone has had sales revenue of $10.283 billion[68] for Gilead, nearly equaling in a single year the total purchase price of Pharmasset. Including sales of Harvoni, revenue on sofosbuvir for Gilead was $12.41 billion in just 12 months. Gilead has made huge profits from sofosbuvir in less than one year and will continue to own the patent on it through at least 2030.[69] This has grave implications for populations at greatest risk for HCV—racial and sexual minorities, low-income individuals, disenfranchised populations (e.g., people who inject drugs), and (in some cases) the under- or uninsured.

All this is not to deny the groundbreaking achievements pharmaceutical companies have made in science and medicine. Corporations like Gilead have allowed us to advance the fight against the HIV epidemic, to treat and cure numerous other illnesses, and to vaccinate against communicable diseases. But the price of a medication should not be so high that it is virtually inaccessible to the populations that need it most, be it in the United States or around the world. And it should not be so high that it places an unsustainable burden on healthcare systems even in the world's wealthiest nations. Indeed, exorbitant pricing for medications like sofosbuvir continues to move us further away from a national goal of broad access to pharmaceutical products and toward a world in which only the wealthiest can access the best treatments, while others are forced to delay or accept inferior treatment. There must be a better balance between the cost of development and manufacturing, profit margins, and domestic and global public health needs.

There must also be a greater effort—whether on the domestic level through negotiations between countries and pharmaceutical companies or on the international level through modifying current intellectual property systems—to ensure broader access to generic drugs for countries that are frequently excluded from discounted drug pricing agreements. In the fight to gain access to affordable HCV treatment, countries with some of the largest HCV epidemics around the world are being left behind. A change must be made.

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