Hepatitis C: The New Battleground for Access to Essential Medicines

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The current revolution in the treatment of hepatitis C brought about by the introduction of new direct acting antiviral agents (DAA) such as sofosbuvir and simeprevir could change the lives of the 130 to 150 million people on the planet living with hepatitis C. While the efficacy of combination regimens including sofosbuvir varies across the different genotypes of the hepatitis C virus (HCV), the success rate is between 70% and 90% in disease caused by the most prevalent genotypes. The new DAAAs also offer clear advantages in terms of side effects, ease of use and duration of treatment.

The new generation of antiviral drugs offers real hope of survival and quality of life to patients who can afford them. Unfortunately, they are a minority.

Although diagnosis, cost of treatment infrastructure and a lack of trained professionals can be problematic in many countries, the key barrier to treatment is the price of the drugs, which varies from country to country depending on the negotiations between each government and the patent holder, in this case the pharmaceutical company Gilead. While the US government paid $84,000 per course of treatment, it is believed that the Spanish government negotiated a price of around 25,000 per patient. Nonetheless, the high cost of the treatment in Spain led the health authorities to impose criteria restricting administration.

The difficulties faced by the patients and health systems striving to cover the cost of treatment contrast sharply with the unprecedented profits Gilead has reaped from an innovation originally developed from molecules created in publicly-funded research centres. While, in 2014 alone, the global sales of sofosbuvir exceeded $10 billion ($2 billion more than the company paid for the drug), a study by the University of Liverpool showed that a three-month course of treatment of the drug can be produced for just $101. Estimates of the cost of production for a 12-week course of treatment range from $68 to $136.

The company’s strategy may appear coherent from the point of view of its shareholders, but it is totally inconsistent with the fair regulation of a public good such as health.

In this situation, what are the alternatives open to poor patients and health systems?
• One possible response is to simply pay the price negotiated with the patent holder. This has been the most common response to date. Leaving aside ethical considerations, it may be seen as more advantageous to pay the cost of a very expensive drug for a short period than to cover the cost of long-term treatment (which is not necessarily inexpensive) for patients with chronic disease. The situation has, however, forced countries like Spain to impose ‘allocation’ criteria, an ethically questionable and politically explosive practice.

• Another possible course of action is the one chosen by India, where the authorities announced some months ago that the application for a patent for Sovaldi had been denied on the grounds that the molecule is not novel. That decision opened up the possibility that a generic version of the drug could be produced and exported at a price of between $100 and $200 for the three-month course of treatment. It also inspired a similar opposition to the patent in Europe. However, the patent holder fought the Indian decision tooth and nail and, unfortunately, obtained a reversal of the decision at the eleventh hour, subject to appeal.

• Finally, the answer for poor patients in low- and middle-income countries could be found in the distribution of drugs at cheaper prices produced under special exemptions or licences. A few weeks ago, for instance, the Drugs for Neglected Diseases initiative (DNDi) announced an agreement with the Egyptian producer Pharco Pharmaceuticals to develop a therapy to treat all the subtypes of hepatitis C based on a combination of ravidasvir and sofosbuvir. The combination therapy will cost less than $300 per patient and course of treatment.

This report is part of a series published by ISGlobal on topics related to innovation and access to essential medicines. The aim of these papers is to lay the groundwork for an informed debate on this fundamental issue of public interest.
Between 130 and 150 million people are living with hepatitis C, a liver disease caused by infection with the hepatitis C virus (HCV), which can lead to cirrhosis and death if left untreated. Between 4 and 5 million of these patients are coinfected with the human immunodeficiency virus (HIV). Today, 7 out of every 10 patients infected with HCV live in developing countries (China tops the list with nearly 30 million patients, followed by India and Egypt with 18 and 12 million, respectively), but the disease is also taking a heavy toll in some of the richest countries in the world (see Figure 1). In Spain and other developed countries, patients with hepatitis C now number in the hundreds of thousands. Many of these patients cannot be safely treated with the traditional drugs owing to the genotype of their virus or because of medical complications.

It is estimated that HCV infection causes over 500,000 deaths every year. Over 70% of these people lived in middle-income countries and most of them died without ever receiving any effective treatment. Clearly, the fact that an effective treatment, which is available and can be produced at a reasonable cost, is being kept out of the reach of most of the people who need it represents a collective failure.
There are 11 main genotypes and several subtypes of HCV, and these determine the appropriate treatment and its efficacy. The standard treatment for HCV was previously pegylated interferon alpha in combination with ribavirin. The recommended treatment for genotype 1 infection (the most prevalent)—known as triple therapy—consists of the standard combination regimen with interferon and ribavirin with the addition of boceprevir or telaprevir, the first direct-acting antiviral agents (DAA). The problem is that, in the best of cases, the efficacy of these regimens is 70%, and this figure falls to around 20% in patients in the advanced stages of cirrhosis and those coinfected with HIV (a very common situation).3

In a new development, more effective DAA, including sofosbuvir and simeprevir, are now available to combine with the standard regimen. Sofosbuvir (Sovaldi) is recommended in the treatment of infections with HCV genotypes 1, 2, 3, 4, 5 and 6 and is administered in combination with ribavirin, with or without pegylated interferon (depending on the genotype). The duration of treatment is 48 weeks for genotypes 1 and 4 and 24 weeks in the case of genotypes 2 and 3.

The effectiveness of sofosbuvir-based regimens varies according to the genotype, but combination therapy with the new DAA is successful in between 70% and 90% of cases for the most prevalent genotypes. These new regimens also offer a clear advantage in that they are associated with fewer adverse effects and are more convenient to administer.

Thus, the new generation of drugs offers a real hope of survival and quality of life to the patients who can access treatment. Unfortunately, this is only a small minority of those who need it.

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Barriers to Access to Treatment

Although disease diagnosis, cost of treatment infrastructures and the lack of trained professionals are problems in many countries, the key barrier to the treatment of hepatitis C is the high price of the drugs, which varies from country to country depending on negotiations between each government and Gilead, the patent holder.

Sofosbuvir (Sovaldi) received marketing approval from the US Food and Drug Administration on 5 December 2013. The initial price fixed by the pharmaceutical company in the USA was $84,000 per course of treatment (about $1,000 per pill). A representative of the leading pharmacy benefit management company in the USA said that the cost of covering treatment for Medicaid® patients and prison inmates alone at those prices would be as much as $55 billion and described the price as “a tax on all Americans”.

The European Medicines Agency granted a marketing authorisation for the drug on 16 January 2014, not long after the American agency. Although a lack of transparency is a constant in the pharmaceutical sector, it has been estimated that Spain, following negotiations with Gilead, is facing a bill of €25,000 per patient per course of treatment, a price that led the Spanish health authorities to establish criteria restricting administration of the drug. France, the United Kingdom and Germany are paying per treatment prices up to twice as high as Spain and are covering all affected patients. However, the prevalence of hepatitis C is much lower in those countries than in Mediterranean countries, such as Spain, or Eastern Europe.

Box 1
Tiered Pricing and Voluntary Licensing: An Inadequate Response


Gilead, like other companies in the case of other diseases, has established a policy of tiered pricing and voluntary licensing that conforms to the company’s marketing strategy, but it is difficult to see how these measures can resolve the problem of access to the drug. For developing countries, the manufacturer established a price of $2,000 per treatment (14 times lower than the price in Spain and 42 times lower than the US price) and granted a voluntary licence to an Indian generic manufacturing company for the production and distribution of the drug to supply a group of 91 developing countries. However, that agreement excludes most of the middle-income countries where most of those infected live. In Egypt, where almost 12 million people are infected with HCV, the government managed to negotiate a price of $900 per treatment for patients covered by the government healthcare plan, who represent only a part of those affected. But even at this price, the cost of providing sofosbuvir to 100% of the patients affected in Egypt would cost 5 times the country’s national public health budget for 2017.

Box 2
DNDi’s Response: An Effective Treatment for Under $300


In April 2016, the Drugs for Neglected Diseases initiative (DNDi) signed an agreement with the Egyptian generic manufacturer Pharco Pharmaceuticals to develop an effective treatment against all hepatitis C subtypes. The cost of the new treatment—a combination of ravidasvir and sofosbuvir—will be less than US$100 per patient.

If this combination regimen, currently in the final phase of clinical trials, proves effective, the agreement may represent a turning point similar to the start of generic antiretroviral drug production in the 1990s. The introduction of generic antiretrovirals at that time cut the price of HIV/AIDS treatments by 90%, facilitating access to treatment for millions of people, particularly in developing countries.

Pharco has agreed to set the commercial price at US$294 once the new treatment has been approved. At this price, many countries that have been unable to underwrite the cost of treatment with sofosbuvir will be able to provide treatment on a large scale for patients with hepatitis C.

Although DNDi holds the necessary licences to produce the combination treatment in many middle-income countries, the new agreement will exclude others—such as Ukraine, Kazakhstan, Morocco, and Syria—where the organisation is not licensed to manufacture ravidasvir, one of the components of the combination regimen. The success of this uphill struggle will depend on whether DNDi and other actors, such as the Medicines Patent Pool, can obtain the licensing rights for more countries, at least for affected middle and low income countries.
The difficulties affecting health care systems and patients striving to cover the cost of the drug contrast sharply with the unprecedented profits Gilead has reaped from a product it bought from another company, which was originally developed on the basis of molecules created in publicly-funded research centres before being sold into the private sector. The skewed logic of such transactions is a direct result of the monopoly conferred by the rules that currently govern intellectual property. By 2014, global sales of sofosbuvir had exceeded $10 billion ($2 billion more than the company originally paid for the drug) and a study by the University of Liverpool has demonstrated that a 12-week course of treatment can be produced for just $101. It is estimated that the cost of production ranges from $68 to $136 for a 12-week course of treatment.

On the basis of these numbers, many observers have pointed out that Gilead’s pricing policy, rather than seeking to recover the company’s investment and make reasonable profits, is in reality designed to extract maximum profits from the opportunities afforded by its advantageous market position with complete disregard for the consequences for patients with the disease. While this strategy may be comprehensible from the point of view of company shareholders, it is totally at odds with the fair regulation of a public good such as health.

Source: Compiled by authors.

Faced with the dilemma posed by the high cost of the new drug, countries can choose between several courses of action. One possible response, the most frequent to date, is to pay the price negotiated with the patent holder. Leaving aside ethical considerations, bearing the cost of a very expensive drug over a short period may be more advantageous than covering the cost of long-term treatment for chronic patients with other drugs that are not necessarily inexpensive. This argument, which is repeated insistently by Gilead, places patients and national authorities in a hopeless impasse. The crisis has forced countries like Spain to establish specific allocation criteria that restrict access to the new treatment, a response that is ethically questionable and politically explosive (see Box 2).

But the decision to take on board the expense of the more effective short course of treatment (further complicated in the case of EU countries by the failure of the joint procurement initiative and the resulting fragmented negotiations by individual member states) is the choice most likely to weaken the negotiator’s position vis-à-vis the company. European civil society has demanded that the EU negotiate a joint procurement agreement, which would strengthen their negotiating capacity and ensure a lower price. Joint procurement for EU countries is a measure that the European Commission has the legal power and competence to undertake, and it has been suggested by certain member states, such as France.

In the case of the least developed countries, a group automatically exempted from the most pertinent provisions of the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), the margin for manoeuvre is defined by each country’s manufacturing capacity. In Bangladesh, for example, Incepta Pharmaceuticals Ltd, a local pharmaceutical manufacturer, is already producing a generic version of Sovaldi at a price of less than $900 per course of treatment, the lowest price offered by the patent owner to date. It is expected that this generic product will be exported to countries where Gilead has no patent or where the TRIPS flexibilities clearly apply.

A third possible response to the dilemma is the road chosen by India, which some months ago announced that it was rejecting Gilead’s application for a patent for Sovaldi on the basis that the molecule is not innovative enough to warrant such protection. This decision opens up the possibility of local production and the export of generic versions of the drug at a price per patient of between $100 and $200 for a 12-week course of treatment. This process started in 2013 when the Delhi Network of Positive People and the Initiative for Medicines, Access & Knowledge filed a legal opposition to Gilead’s patent. Indian patent law has acquired a reputation for holding strong positions in this arena, which some parties attribute to an interest in protecting the country’s national generics manufacturing industry. Whatever the reason, the decision of the Indian courts will make it possible for patients to access treatment at a cost of less than $900.

The situation was assessed in a press release by the Doctors without Borders Access Campaign:

Gilead has signed voluntary licence agreements with multiple generic drug producers in India, but these agreements impose many restrictions, including which countries can access the drugs produced under these licences, as well as invasive restrictions on medical providers and patients with respect to distribution and use of the drug.

With the patent being denied, other companies that have not signed the licence are now free to produce. Entry by additional generic manufacturers should increase the open competition needed to bring prices down dramatically, especially in those countries that have been excluded from the voluntary licence agreement, and thereby increase access to the medicine.

Gilead will undoubtedly fight tooth and nail to overturn the Indian decision. The company had already put in place stringent restrictions to prevent the “diversion” of generic versions of the drug to wealthier countries. However, it is also possible that India will be successful in maintaining its legal victory.

In a move unprecedented within the EU, the French non-government organisation Médecins du Monde filed a patent opposition in February 2015 challenging the registration of one of Gilead’s sofosbuvir patents at the European Patent Office. They argued that while the use of sofosbuvir to treat hepatitis C is undeniably a therapeutic advance, the molecule itself does not merit a patent because it relies on existing and commonly practised techniques in the pharmaceutical field.

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**References**


Although Gilead and other companies have other sofosbuvir patents pending approval that could neutralise the effects of this opposition, the decision taken by Médecins du Monde is unprecedented in Europe and has given rise to a succession of similar legal initiatives (see Table 1). The breach opened by the case in India could help in a suit that has been designed by the same team of lawyers.

Finally, activist organisations and political groups in several countries have asked their governments to issue a compulsory licence immediately. Such licences exempt the company from respecting the patent for reasons of public interest (in this case a public health emergency) and would allow local production of generic versions of the drug. Compulsory licensing is one of the flexibilities specified in the World Trade Organisation’s TRIPS agreement, although it has only been invoked on very few occasions to facilitate access to medicines, and to date always by poor countries. Under the terms of a compulsory licence, the government would have to pay remuneration to Gilead, but the amount would be much lower than the price they are obliged to pay for the patented drug on the commercial market.

Box 3
Spain: the Problem in a Microcosm

An estimated 700,000 people in Spain have hepatitis C and, of these, 50,000 are in the advanced phase of the disease. Many patients could not be treated safely with the standard treatments because of the genotype of their infection or owing to other complications.

Initially, the Spanish health authorities allocated a budget of 125 million for the purchase of sofosbuvir (marketed by Gilead as Sovaldi) at a price estimated to be around 25,000 for each 12-week course of treatment (the actual figure has never been made public by the Spanish Ministry of Health). Such an allocation would have covered the cost of treating 5,000 patients in 2015, falling far short of covering the real needs. The decision was denounced by patient associations, which mobilised all over the country throughout 2015. Some groups demanded an increase in the budget allocation and others called for the issue of a compulsory licence. The Spanish government promised to implement a national plan for the treatment of hepatitis C that would determine the number of patients affected and would then decide on the scientific criteria that would be used to decide which patients should receive treatment.

The broad outlines of that plan were presented at the end of February 201515. The plan recommended using the drug at lower price, a ceiling of 727 million was fixed (an amount distributed in the form of loans to the country’s regional governments). Furthermore, the number of patients filling the established criteria exceeded 50,000, an indication that the plan will not cover current needs.

As has happened in other countries, the debate in Spain has shifted slowly away from budget cuts towards questioning the justification for the price set by the pharmaceutical companies. Initially, professional associations, patient advocacy groups and political parties focused on demanding a larger budget to fund treatment; however, many people now call into question an approach driven solely by the commercial strategy of the patent holders. Spain was not particularly active in the European negotiations for a joint procurement agreement and withdrew from the discussion at an early stage.

References


Hepatitis C has achieved more international attention than ever as a result of the controversy surrounding the difficulty of accessing the latest treatments, even in wealthy countries. Initiatives such as UNITAID and Medicines Patent Pool, originally established to speed up the development of drugs for HIV/AIDS, tuberculosis and malaria and increase access to such treatments, have now incorporated the development of new diagnostic methods and treatments for hepatitis C into their area of action. Likewise, organisations that have historically denounced the lack of access to treatments for AIDS are now also raising their voices about the lack of adequate treatments for hepatitis C and the high rate of new infections. The situation has been further exacerbated by the fact that most middle-income countries, where the majority of those infected reside, were excluded from Gilead’s voluntary licensing deal and that most of them defend the right of countries to issue compulsory licenses.

Overall, the debate has followed a path remarkably similar to that of the discussion fifteen years ago about treatments for HIV/AIDS: first the companies try to impose their prices, and then they propose a deficient differential pricing policy; finally, the countries with sufficient political clout come to the conclusion that the company’s policy is inadequate and decide to take unilateral action. This is what India has done and it is not out of the question that Europe may decide to take similar steps to ensure adequate coverage of the population in need (changes in the current policy are not out of the question).

The category of patients vulnerable to the lack of drug access is no longer defined by the traditional borders separating the wealthy and the developing world; today, it transcends geographical boundaries. People in Spain are experiencing the same situation that is affecting hundreds of millions of patients all over the world. However, notwithstanding the importance of the issue, hepatitis C is not the only problem affected by the model of pharmaceutical innovation. And rigid interpretation of the rules of intellectual property is not the only challenge that must be faced. Antimicrobial resistance, which ISGlobal will analyse in another case study, illustrates another flaw in the current system, one that is very different, but just as worrying.

The fact that we have advanced in such an unequal way over the fifteen years since the HIV/AIDS crisis demonstrates the extent to which the model of innovation and access is in need of a complete overhaul—a reform going beyond quick fixes for specific diseases or populations. At the very least, we need new incentives that would make it possible to align the priorities of innovation with those of the interests of the broader public.
References


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