

## Public procurement of hepatitis C medicines in Brazil from 2005 to 2015

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**Abstract** *This paper analyzes the Minister of Health's (MoH) procurement of medicines for hepatitis C from 2005 to 2015. Data sources were the Integrated General Services Administration (SIASG), to estimate annual expenditure for selected medicines of the MoH Clinical Protocols and Therapeutic Guidelines (PCDT) for Hepatitis C. All presentations and strengths recorded on SIASG were included. The unit prices were estimated based on the purchase with the highest volume each year. There was a 159.5 fold increase in expenditure of the selected medicines from 2005 to 2006, because procurement of those medicines became centralized. In 2007 there was 730% increase in spending due to the incorporation of peginterferons alfa 2a and 2b. In 2012 the purchase of only two new direct-acting antivirals (DAA) accounted for 99% of total annual expenditure. In 2015 the adoption of a new DAA led to an increase of 230% (R\$945 million) in MoH spending. The significant increase of MoH expenditure on medicines for hepatitis C from 2005 to 2015 was due to the increase of volumes purchased as well as the incorporation of alfapeginterferon and new DAAs. Ensuring universal access to treatment for hepatitis C will depend on the implementation of strategies that strengthen the MoH's bargaining power in price reduction negotiations with the manufacturers of monopoly medicines.*

**Key words** *Health economics, Pharmaceutical services, Hepatitis C, Medicines procurement*

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## Introduction

Every year around 1.4 million deaths occur worldwide due to causes related to viral hepatitis<sup>1</sup>. An estimated 500 million people are living with chronic hepatitis B and C virus infection. Viral hepatitis has been considered an invisible epidemic that affects all countries irrespective of income level.

In 2010, the World Health Assembly (WHA) recognized viral hepatitis as a global public health problem (WHA 63.18)<sup>1</sup>. In 2012, the World Health Organization (WHO) proposed a plan of action for the prevention, health care and control of viral hepatitis in order to raise awareness about the problem<sup>1</sup>. At the 2014 WHA a new resolution was approved, urging all WHO Member States to adopt and/or strengthen appropriate actions to prevent transmission of the six types of hepatitis virus, as well as to provide appropriate care / treatment to those in need<sup>2</sup>.

The clinical presentation, severity and disease progression or not to chronic liver disease, depends on the type of virus involved, as well as on the actions implemented to control and treat the infection. Hepatitis A, B and C are the most prevalent types in the world. The first is transmitted by ingestion of water or food contaminated with fecal material. Hepatitis B can be transmitted through unprotected sexual intercourse and/or blood contact from an infected person, and may progress to chronic forms of liver disease. Hepatitis C is mainly transmitted through contact with contaminated blood and usually evolves quietly to chronic hepatitis. There are effective vaccines for hepatitis A and B, but not for hepatitis C<sup>3</sup>. Hepatitis B can be transmitted through sexual or blood contact with an infected person. It may progress to chronic forms of liver disease. Hepatitis C is mainly transmitted through contact with contaminated blood and usually evolves quietly and slowly to chronic hepatitis.

Chronic hepatitis B and C should be treated with medicines that suppresses viral replication, which reduces the disease progression to more severe outcomes, such as cirrhosis and liver carcinoma.

Since the 1980s, viral hepatitis have been apriority for health authorities in Brazil. From 1996, viral hepatitis is compulsory notifiable disease to SINAN (National System for Diseases Surveillance. This is a key information source for MoH authorities to design policies for prevention, treatment and control of hepatitis<sup>4,5</sup>.

Since 1998, in addition to actions aimed at structuring the network of diagnostic and

treatment health services, universal vaccination against hepatitis B has been established. Initially, all newborns and children under one year of age were vaccinated. Currently vaccination covers all persons under 49 years-old.

Initially, the treatment provided for Hepatitis C was conventional alfainterferon 2a and 2b monotherapy. These medicines used to be purchased by the Brazilian states and co-financed by the MoH<sup>4</sup>. Then, the treatment protocol adopted also included a combined treatment regimen with peginterferon alfa 2a or 2b plus an antiviral<sup>6,7</sup>.

In 2000, the first clinical guideline for hepatitis C was published, which recommended the use of dual peginterferon 2a or 2b plus ribavirin regimen<sup>8</sup>. In 2002, the National Program for the Control of Viral Hepatitis was established (Ordinance MS263 / 2002)<sup>9,10</sup>. In 2009 the program was incorporated into the Department of Sexually Transmitted Diseases, Aids and Viral Hepatitis<sup>11</sup>.

Currently the treatment of hepatitis C is undergoing an important transformation, in which new medicines, known as direct-acting antiviral drugs (DAA), administered orally, are available or are in final stages of development (clinical studies)<sup>12</sup>. In May 2015, WHO included five DAAs in its Model List of Essential Medicines<sup>13</sup>, which has been a guide to decision-makers at country-level. They are sofosbuvir, simeprevir, daclatasvir, desabuvir and the fixed dose combinations ledipasvir + sofosbuvir and ombitasvir paritaprevir + ritonavir.

These medicines are under monopoly, because pharmaceutical companies have applied for patent protection in different countries<sup>14</sup>, in the widespread global adoption of intellectual property protection under the Agreement on Trade Related Aspects of Intellectual Property Rights of the World Trade Organization (WTO TRIPS Agreement). Patent protection of products may occur in almost every country in the world including those with the ability to produce generic versions. Thus, these companies are in a position to define prices. The huge potential lucrative global market is the main factor that has driven the development of the new DAAs. The price of these new medicines challenges the ability to purchase of developed and developing countries and their capacity to respond to the epidemic as set out in international commitments<sup>15,16</sup>. Therefore, treatment of hepatitis C is a model case study of the incorporation of monopoly products into public and private health systems, in which the increasing costs threatens the sustainability of policies to ensure access to treatment.

In 2012, the first DAA boceprevir and telaprevir<sup>17</sup> were incorporated into the treatment guideline provided by the Brazilian MoH. In 2015, simeprevir, sofosbuvir and daclatasvir were approved by the National Agency of Sanitary Surveillance (Anvisa) and incorporated into the MoH hepatitis C treatment guidelines<sup>18</sup>.

This paper objective is to analyze the evolution of MoH purchases of hepatitis C medicines from 2005 to 2015, based on estimates of annual contracted expenditure, direct costs of treatment, and a comparison between prices paid in Brazil and available international reference prices.

## Methodology

A descriptive analysis of MoH hepatitis C medicines purchases in the period 2005 to 2015, using as the data source the MoH purchases records made by the MoH logistics sector in the Integrated System of Administration of General Services (SIASG). It is a system in which all contracted government purchases from the federal public administration are recorded. We considered the quantities purchased per year and the prices of each purchase. Estimates of the annual contracted expenditure were made for a list of selected medicines incorporated into the MoH Clinical Protocol and Therapeutic Guidelines (PCDT) for Hepatitis C<sup>6,17</sup>. It included all presentations and strengths recorded on the SIASG. Prices paid

in reais (R \$) were adjusted by the National Extended Consumer Price Index (IPCA) from 2015 to better allow for time series comparisons. The same PCDT were used to calculate the direct costs of treatment regimens (Chart 1). Values obtained were converted to the average dollar (US \$) each year.

For the schemes involving INF and ribavirin, estimates of dose and amount of pharmaceutical units per day were based on an individual of 60-65 kg with chronic hepatitis caused by HCV genotype 1, whose prevalence in Brazil is about 60%<sup>19</sup>. The unit price considered was the one obtained in the purchase of larger volume each year. The volume of each product was presented in pharmaceutical units.

Finally, in relation to the DAA incorporated in 2015, the cost of treatment paid by the Brazilian MoH, based on direct purchases with multinational companies, was compared with available international reference prices. The treatment costs of SOF + DAC and SOF + SIM combinations were compared. For the SOF + DAC combination, the following prices were considered for sofosbuvir: the Brazilian price of US\$ 6,376 for 12 weeks of treatment and the reference price of Egypt<sup>16</sup> of US\$ 900 for 12 weeks of treatment, and the price of a generic version available in India in 2015 of US\$ 483 for 12 weeks of treatment<sup>21</sup>. For daclatasvir, the price paid by the Brazilian MoH was US\$ 2,365 for 12 weeks of treatment, and the generic version available in

**Chart 1.** Therapeutic regimen adopted for the estimates of treatment costs, 2011-2015.

	Regimen	Duration of treatment	Total of units per treatment
1*	ALFA-PEG-INF 2a 180ug once a week + RBV15mg/kg/day (4 tablets/day)	48 weeks	48 bottles (ALFA -PEG-INF 2a) 1,344 capsules (RBV)
2*	ALFA-PEG-INF 2a 180ug once a week + RBV15g/kg/day (4 tablets/day)	72 weeks	72 bottles (ALFA -PEG-INF 2a) 2,016 capsules (RBV)
3*	ALFA -PEG-INF 2a 180ug once a week + RBV15mg/kg/day (4 tablets/day) +TPV 375mg (dose diária, 2 tablets, 3x/day)	48 weeks	48 bottles (ALFA -PEG-INF 2a) 1,344 capsules (RBV) 504 tablets (TPV)
4*	ALFA -PEG-INF 2a 180ug once a week + RBV15mg/kg/day (4 tablets/day) + BCV cápsula 200mg (daily dose, 4 capsules, 3x/day)	48 weeks 44weeks	48 bottles (ALFA -PEG-INF 2a) 1,344 capsules (RBV) 3,696 capsules (BCV)
5**	SOF tablet 400mg (1 tablet/day) + DAC tablet 60mg (1 tablet/day)	12 weeks	84 tablets (SBV) 84 tablets (DAC)
6**	SOF tablet 400mg (1 tablet/day) + SIM capsule 150mg (1 tablet/day)	12 weeks	84 tablets (SBV) 84 capsules (SIM)

\* PCDT, 2011<sup>6</sup>\*\* PCDT/MS, 2015<sup>20</sup>.

ALFA-PEG-INF 2a – Alfa peginterferon 2a/ RBV – ribavirin/TPV –telaprevir/ BCV – boceprevir/SOF – sofosbuvir/ DAC – daclatasvir/SIM – simeprevir.

India in 2016 was US\$ 183 for 12 weeks of treatment<sup>22</sup>. No reference price information for daclatasvir previous years was found 2016. For the SOF + SIM combination the price paid in Brazil in 2015 for SIM (US\$ 2,426 for 12 weeks of treatment) was used and the three above mentioned price options for SOF. No international reference price was found for SIM generic version.

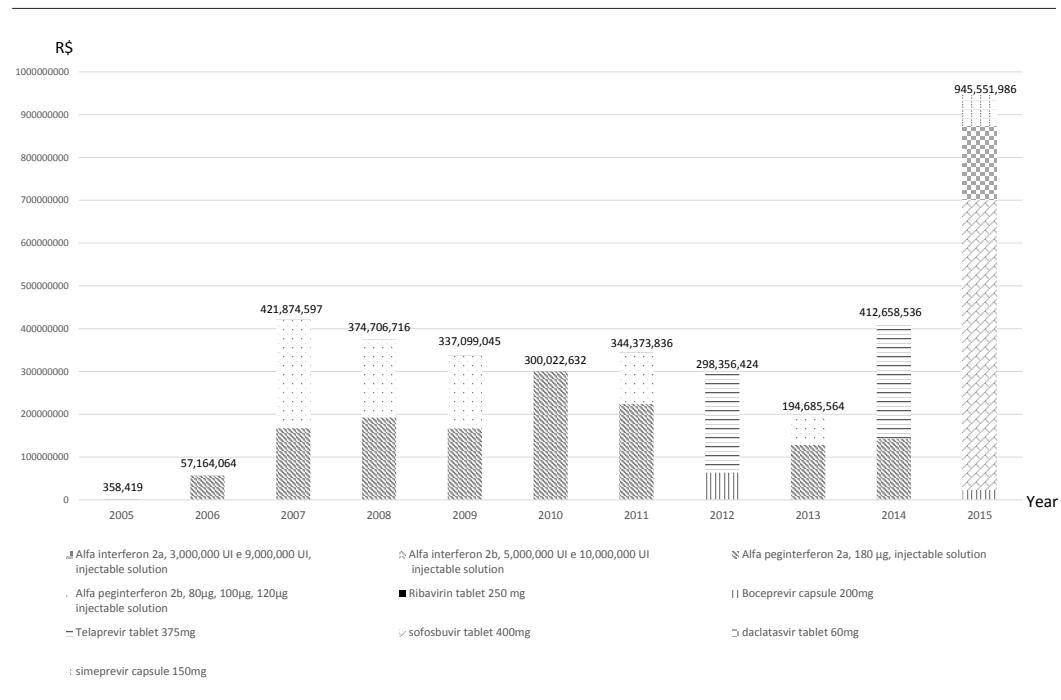
## Results

There was a 159.5-fold increasing in spending on selected medicines from 2005 to 2006 ranging from R\$ 358,418.7 to R\$ 57,164,064.5. Centralized purchasing of hepatitis medicines was implemented by the MoH in 2006 (Graph 1) when monetary purchases of peginterferon 2a accounted for 97.7% of the total purchase. In 2007, there was an increase of almost 7.4 times in the contracted expenditure, mainly due to the purchase of peginterferon alfa (2a and 2b in different strengths), which represented 99.9% of that year's expenditure (Graph 1).

From 2008 to 2010, price reductions were observed in contracted expenses due to reductions

in the volume of peginterferon 2a and 2b pharmaceutical units purchased (608,357 in 2008, 539,291 in 2009 and 540,000 in 2010, Chart 2). It is noteworthy that in these three years, the purchase of peginterferon 2a and 2b accounted for 99.9% of annual contracted expenditure. In 2011 there was a significant increase in expenses related to peginterferon 2a and 2b, jointly with an increase in volume (898,479 pharmaceutical units). In 2013, the volume for these products was similar to that of 2008 (639,717). There was a reduction in expenditures related to peginterferon alfa 2a and 2b purchases, with spending decreased respectively from R\$ 421,838 million in 2007, R\$ 374,685.7 million in 2008 and R\$ 194,657.8 million in 2013. These results show that, despite the increasing in volume purchased, prices have gone down.

Two new medicines introduced in 2012, telaprevir and boceprevir, had contracted expenses of R\$ 298,283.9 million, which corresponded to 99.9% of the total purchases of the MoH for hepatitis C medicines that year (Graph 1). This result illustrates the burden of these medications on the MoH expenditure. In 2013, there was a 34.7% reduction in spending for hepatitis C compared to



**Graph 1.** Estimates of contracted expenditures of the Ministry of Health (in BRL) for hepatitis C medicines. Brazil 2005-2015.

\*Adjusted for inflation (2015 IPCA).

**Chart 2.** Volume (in number of pharmaceutical dosage forms) of medicines for hepatitis C procured by the Ministry of Health. Brazil, 2005-2015.

Name and Dosage Form	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Alfainterferon 2a, 3.000.000 UI, injectable solution		96	72	78	234				420	120	
Alfainterferon 2a, 9.000.000 UI, injectable solution	720	2,172			20						
Alfainterferon 2b, 5.000.000 UI, injectable solution		234						40			
Alfainterferon 2b, 10.000.000 UI, injectable solution	12										
Alfa peginterferon 2a, 180µg, injectable solution	24	64,821	194,056	312,537	224,734	540,000	630,805	35	415,995	537,075	
Alfa peginterferon 2b 80µg, injectable solution	40	179	186,849	236,724	195,401		128,020		126,981		
Alfa peginterferon 2b 100µg, injectable solution		146	80,395	44,450	101,041		100,295		72,646		
Alfa peginterferon 2b 120µg, injectable solution	12	24	29,514	14,646	18,115		39,359		24,095		
Ribavirin tablet 250 mg	1,320	17,868	27,780	10,500	5,520	2,280	3,000	1,860			
Boceprevir capsule 200mg								4,638,480			1,807,344
Telaprevir tablet 375mg								2,145,696		3,024,000	
sofosbuvir tablet 400mg											2,684,304
daclatasvir tablet 60mg											1,834,056
simeprevir capsule 150mg											736,848

2012. In that year, there was no purchase of DAAs and 100% of the MoH expenditures were relat-

ed to the purchase of peginterferon 2a and 2b. In 2014, expenditures returned to 2007 levels. The

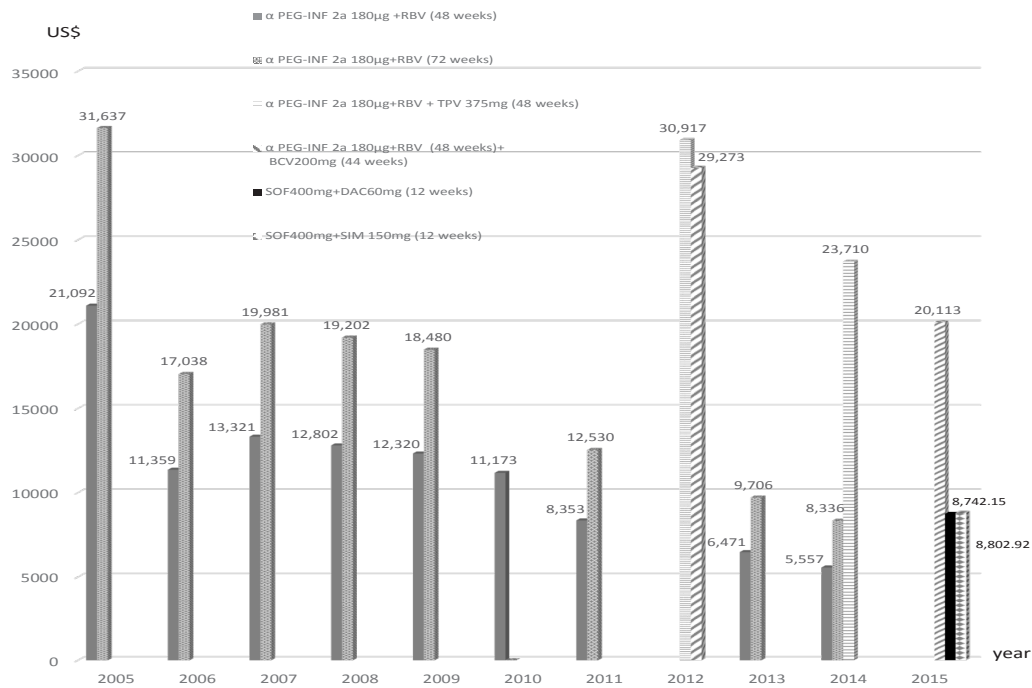
purchase of telaprevir accounted for 65% of that annual expenditure while the purchase of peginterferon accounted for 34%, indicating change in the annual purchases of the higher expenditure products. In 2015, there was a change in the profile of purchases and contracted expenses, which increased 2.3 times in relation to total purchases in 2014, reaching a total of R\$ 945.5 million. It is noteworthy that this value refers to the spending in relation to four DAA: sofosbuvir, simeprevir, daclatasvir and boceprevir.

In relation to estimates of the treatment direct costs with the combination of peginterferon 2a + RBV for the 48 and 72 week regimens, a reduction was observed during the study period, reaching in 2014, values of US\$ 5,557 and US\$ 8,336 (Graph 2), respectively. From 2012 on, the traditional treatment regimen (double therapy) started to include a DAA (IP), telaprevir or boceprevir (triple therapy), the estimated treatment cost increased to US\$30,917 and US\$ 29,273, respectively (Graph 2).

In order to compare treatment costs and direct costs of therapeutic regimens involving SOF, DAC and SIM, reference prices from Brazil were used as follows: (i) sofosbuvir + daclatasvir - US\$ 8,742 (ii) sofosbuvir+simeprevir - US\$ 8,803. Comparisons with international prices (Egypt and Indian generics) treatment schemes show costs could have been lower by 62.6% to 92.4% for SOF+DAC and by 62.2% to 67% for SOF + SIM regimen (Graph 3).

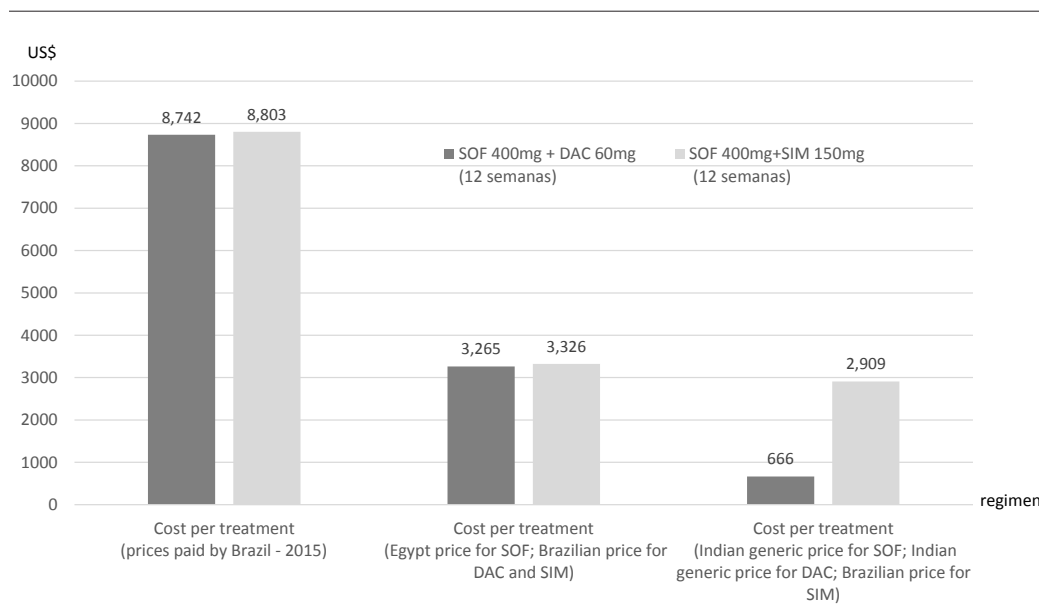
## Discussion

This study demonstrates that during the study period there was an increase in MoH spending for hepatitis C treatments. The data shows that the increase was initially due to the centralization of the purchases and incorporation of peginterferon, and later, due to the incorporation of new DAAs. There was an increase in the volume of pharmaceutical units acquired over time, but also



**Graph 2.** Cost of treatment estimates (USD) for hepatitis C. Traditional regimens and adoption of DAA. Brazil, 2005 a 2015.

Source: Prices obtained from SIASG. The following exchange rates were considered: 1 USD = 2.4352 BRL (2005); 1 USD = 2.1761 BRL (2006); 1 USD = 1.9479 BRL (2007); 1 USD = 1.8346 BRL (2008); 1 USD = .9976 BRL (2009); 1 USD = 1.7603 BRL (2010); 1 USD = 1.675 BRL (2011); 1 USD = 1.954 BRL (2012); 1 USD = 2.1576 BRL (2013); 1 USD = 2.3534 BRL (2014); 1 USD = 3.3315 BRL (2015).



**Graph 3.** Comparison of treatment cost estimates (USD) from prices paid by Brazil vs international reference prices for sofosbuvir (2015) and daclatasvir (2016).

during the period studied the volumes purchased of peginterferon were progressively reduced, while the volumes purchased of new DAAs significantly increased.

From 2006 onwards, in order to reduce expenses, the MoH have implemented centralized purchasing of hepatitis medicines (Ordinance 562 / GM, 2006)<sup>22</sup>. The increase in volume and expenditure of purchases in 2005 and 2006 shows the burden of the incorporation of peginterferon for the treatment of hepatitis C. As shown in Chart 2, the volume of purchases of peginterferon became higher in subsequent years, when compared to purchases of conventional INF, suggesting a preference for the first option over the second, and illustrating the effect of incorporation of new medical technologies. In the same period, there was a reduction in the direct cost of treatment, due to the price of the therapeutic regimen adopted. Thus, even with the increase in the volume of purchases, the total expenses did not increase. This suggests that the centralization of purchasing had a positive effect on the reduction of the unit price of peginterferon 2a and 2b.

Centralized procurement, as happened for ARV<sup>24</sup> and imatinib mesylate<sup>25</sup>, was an important strategy for reducing the price of alfa peginterferon in a context of increasing access to treatment in the country, probably due to the stronger bargain power of the MoH given its capacity to purchase greater volume of medicines<sup>26</sup>.

Moreover, the significant reduction in the cost of treatment with peginterferon (Graph 2) may reflect some strategies adopted by the MoH such as: better price negotiation with manufacturing companies; Competition between the two peginterferon options; and the expectation that a new DAA will be launched in the international market. Alfa peginterferon 2a is supplied by Roche and 2b by Shering-Plough. As there is no therapeutic difference between between alfa peginterferon 2a and 2b, the difference occurs in the number of units administered, which is greater for the 2b because of the differences in concentration.

In the case under analysis it can be assumed that the lower unit price, together with the purchased volume (70%) of alfa peginterferon 2a, in 2011, may have influenced the price reduction verified in 2013 for peginterferon 2b.

From 2013 on, new DAAs have been launched in the international market. There are a large number of compounds in the final stage of development (clinical trials), which means potential availability of new products in the coming years. Among those already approved by the FDA are sofosbuvir, simeprevir, daclatasvir, ombitasvir, ledipasvir, dasabuvir, ABT-450. The first three have already been incorporated to the WHO treatment guidelines for Hepatitis C<sup>27</sup>.

The landscape of the hepatitis C treatment with the new DAA medicines indicates a signif-

ificant change both from the clinical and the use point of view. Clinical studies involving combinations of DAA has demonstrated high efficacy, as measured by sustained viral load reduction (SVR), reaching values up to 100%<sup>12</sup>, and pointing to an interferon-free therapy scenario. From the use perspective, the new DAAs favor treatment, because they are orally administrated and shorter duration of treatment, for example 12 weeks, than previous regimens using interferon. Changes in treatment regimens and their effects are highlighted in two moments, marked respectively by the incorporation of peginterferon in 2005 and the DAAs in 2012, when there was a significant increase in MoH expenditure. In the first, the benefit in improved patients adherence to treatment due to reduction in the number of doses administered (from 3 times a week with conventional alfa interferon to one time a week with alfa-peginterferon). In 2012, the incorporation of two DAAs - boceprevir and telaprevir - for the treatment of hepatitis C cases with advanced fibrosis, and not responsive to the previous regimens, accounted for 98% of purchases that year. Compared with the previous regimen, the increase observed in the individual cost of treatment (Graph 2) was significant and has considerably changed the profile of MoH spending on hepatitis C as of 2012.

According to the 2013<sup>17</sup> MoH guidelines, treatment with telaprevir and boceprevir indicated only for hepatitis C patients with advanced stages of liver disease (metavir F3 and F4). In 2012 the purchase of great quantity of these medicines resulted in significant increase of the MoH expenditure. This is because between 2012 and 2014, as shown in Graph 1, the purchase of these two DAA accounted for almost all of the financial resources available for hepatitis C medicines. In 2012, the volume measured by the number of treatments purchased were 1,255 and 4,257 treatments for boceprevir and telaprevir respectively. This may mean that the number of patients eligible for treatment with these DAAs in the country was probably higher due to late detection of the disease.

In 2015, treatment options were further amended, when the National Commission for the Incorporation of Technologies in SUS (Conitec) approved the incorporation of sofosbuvir, simeprevir, daclatasvir, and recommended the adoption of interferon-free regimens for specific cases such as advanced hepatic fibrosis (metavir F3 or F4); F2 liver biopsy for more than three years; HIV / HCV coinfection; pre and post transplantation of liver and other specific indications<sup>28</sup>.

The purpose of incorporation is to ensure the best treatment for all. When Conitec recommends incorporation, it does not limit its analysis to therapeutic evidence; it also examines the impact of technology on the health system, considering the need to ensure treatment for those who need it. The incorporation of the technology must be linked to the therapeutic guidelines, for two reasons: first, the therapeutic guidelines that, according to the WHO, supports the medicine indication and therefore its selection; Secondly, because the Brazilian Decree 7,508/12 establishes that medicines within the SUS should be prescribed according to existing therapeutic guidelines<sup>29</sup>. The incorporation of the DAAs led to the revision of the PCDT in 2015<sup>20</sup>.

Once the effectiveness of interferon-free regimens was confirmed, it is essential that they are guaranteed for all, because they are treatments with high success rates and cure a slow-onset disease but with high morbidity rates<sup>28</sup>.

In relation to prices, the process of purchasing medicines for hepatitis C should consider the dynamics of the medicines marketing, production and patent issues. Moreover, the market dynamics for these medicines in developing countries points to opportunities for price reduction. In Brazil, the treatment costs for the combinations of sofosbuvir + simeprevir and sofosbuvir + daclatasvir were in 2015 respectively US \$ 8,803 and US \$ 8,732. The MoH claims to have achieved significant price reductions when compared to prices in developed countries or to previous schemes involving TPV and BCV. However, the reductions achieved were insufficient and may compromise the universalization of access and the financial sustainability of the response to hepatitis C, especially with the possibility of a SUS funding freeze for 20 years<sup>30</sup>.

It is worth highlighting that the change in therapeutic regimens meant that the estimated expenditure went from around R\$ 412 million in 2014 to around R\$ 945 million in 2015. Assuming that the purchase is a proxy for use, we estimate that this expenditure covered the treatment of around 30 thousand people. In Brazil, it is estimated that 1.4-1.7 million people are infected with HCV<sup>31</sup>. Assuming that 1.4 million of these people were eligible for the SOF + DAC association (US \$ 8,732), the resource needed to treat them all would be US\$12.2 billion or R \$ 40.7 billion. In 2014, the total expenditure of the MoH with medicines was R\$ 12.4 billion<sup>32</sup>.

The scaling up treatment for chronic hepatitis C therefore depends on the MoH develop-



ment of strategies that strength its bargaining power to negotiate price reductions for monopoly medicines.

After 2005, countries with manufacturing capacity to produce generic medicines had to comply with the TRIPS Agreement, which establishes patent protection for pharmaceutical products. In addition, multinational corporations, mostly patent holders, have entered into voluntary licensing agreements with Indian generic manufacturing companies, which have ensured market segmentation and have restricted access to the cheaper alternatives to a limited number of countries. Many middle-income countries, including Brazil, are unable to import these cheaper alternatives generic versions<sup>33</sup>.

Despite the difficulties and barriers mentioned above, it is possible to identify some options that the MoH could seek to strengthen its bargaining power when negotiating the prices of medicines under monopoly for viral hepatitis, as is illustrated by an analysis of the case sofosbuvir. The first step is to identify the patent barrier, ie what are the product patent applications filed in the country and analyze their patent status (pending or granted). According to the WHO patente landscape<sup>34</sup>, there are at least 21 patent claims applications related to sofosbuvir, of which at least five are filed in Brazil.

The next step is to qualitatively analyze the patent applications filed in order to screen those applications that actually cover the active principle ingredient (compound), production processes and available presentations, as well as to identify those that are just strategies to generate uncertainty around the product's patentability. The primary focus must be on the patent applications that can actually guarantee the exclusivity of the product purchased by SUS.

When the patent applications are pending a decision on whether or not to grant a patent, the MoH is able to import cheaper generic alternatives. If the option is to ensure more clarity as to whether or not to decide on patentability, two approaches can be implemented: the presentation of pre-grant oppositions (in Brazil is called "support to examination", according to article 31 of the Brazilian industrial property legislation), and the request for priority examination to the INPI, as established in Resolution 80/2013 of this body<sup>35</sup>. In 2015 and 2016, civil society organizations and national companies submitted oppositions related to patente applications for SOF in Brazil<sup>36</sup>. In 2016, the MoH requested priority examination of DAA patent applications, including those related

to sofosbuvir.

If relevant patent applications are granted in the country, it is then appropriate to explore other options. From the perspective of industrial policy and local production efforts, one option is to use flexibilities such as "experimental use" and "Bolar exception" to obtain the registration (market authorization) for generic versions. This would enable the government to estimate production costs, have better references on the mark ups of the pharmaceutical companies, and to help the government in the issuing of compulsory licenses if price negotiations are not satisfactory<sup>37</sup>. This strategy can also be adopted while patent applications are pending decision.

Another strategy to be considered is the use of reference prices in the international market. These prices can be used by countries with the same level of relative development, for instance, Brazil could ask for the prices for SOF sold in Egypt and India. If the option to issue a compulsory license is used, it is important to identify international sources of the generic medicine which can be imported, as well as identifying capacity for local production by national public or private manufacturers. In 2016, Fiocruz announced a partnership with a consortium of national private companies for the development of sofosbuvir<sup>38</sup>.

Considering the dynamics of incorporating new medicines into the SUS as well as the number of stakeholders with which the MoH has to establish price negotiations each year, the challenge is to build strategies that enable the government to strengthen its bargaining power. It is opportune to identify the governmental institutions and stakeholders that can act in the different aspects of regulation of monopoly and price setting in order to contribute to the sustainability of the access to treatment for hepatitis C in SUS<sup>39</sup>.

The following examples are illustrative of the role that different institutions can play in order to make relevant medicines available and affordable in the country. Anvisa could contribute to the regulation of entry prices (CMED) as well as to the mapping of patent applications and patent status and in the qualification of available products in the international market in case importation is needed; the Oswaldo Cruz Foundation could contribute in the elaboration of patent oppositions (support to the examination) of relevant patent applications, as well as in the development of medicines, and to provide the MoH with estimates of cost of production; the MoH could request priority examination of the rele-

vant product patent applications, as well as coordinate the different strategies involving governmental, non-governmental and private actors.

Some limitations of this analysis are: first, some selected medicines are also used for the treatment of hepatitis B, which may in turn make it difficult to accurately estimating the number of treatments; another issue concerns the currency exchange rate used. For imported products, such as the DAAs, the purchase contracts use different currency exchange rates that are only defined at the time of payment. Third, since the study is based on committed purchases and on contracted expenditure, exchange rate changes may have influenced the cost estimates. Fourth, the comparison with international prices was partially compromised by the fact that generic versions of simeprevir were not identified until the time of completion of the study, and only one source for generic version of daclatasvir was identified in 2016.

### Final considerations

The study shows changes in the profile of MoH purchases for hepatitis C medicines, up to 2011,

due to the incorporation of peginterferon alfa 2a and 2b, and afterward to the incorporation of new DAAs, which are more expensive medicines. If, on the one hand, new medicines have a better effectiveness profile than the previous options<sup>12,13</sup>, on the other hand, the prices paid by the Brazilian MoH put at risk the possibility of treating everyone, compromising the principle of universal access under SUS. High drug prices should not be the justification for not treating everyone in need. Faced with this impasse, it is necessary for the country, that the MoH finds ways to deal with prices determinants that negatively impact on spending, by implementing a set of strategies to strengthen its bargaining power in price reduction negotiations, including addressing patent barriers and developing strategies for local production.

This analysis of expenditures and the estimated direct costs for the treatment of hepatitis C, provides an important basis for a more in-depth analysis of the challenge faced in Brazil of increases in expenditures on medicines for SUS, increased burden of diseases and the pressure to incorporate innovative and monopoly technologies.

### Collaborations

GC Chaves conceptualized the study, retrieved data, developed methods, analysis and first draft. MA Oliveira participated in analysis, drafting and review of manuscript. CGC Osorio de Castro was responsible for data curation, participated in critical review of data, drafting and review of manuscript. All authors approved the final version of the manuscript.

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**Errata****p. 2527****where it reads:**

Claudia Garcia Serpa Osorio de Castro

**reads up:**

Claudia Garcia Serpa Osorio-de-Castro

**p. 2536****where it reads:**

CGC Osório de Castro

**reads up:**

CGC Osorio-de-Castro