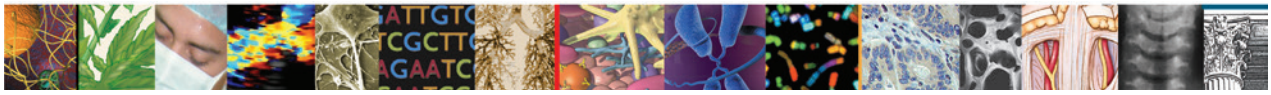

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Perspective

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# Brazil's Fight against Hepatitis C — Universalism, Local Production, and Patents

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The emergence of new direct-acting antiviral drugs (DAAs) has revolutionized the treatment of hepatitis C virus (HCV); these more effective and better tolerated drugs allow for cure rates exceeding 90%. The price of these new therapies, however, is prohibitive in many countries, so creative strategies are needed for ensuring access. Brazil, a pioneer in the fight against HIV/AIDS, is now at the forefront in addressing HCV. The country's strategy, which combines evidence-based treatment protocols and innovative initiatives for local production of generic DAAs, needs to be considered in light of ongoing conflicts over pharmaceutical patents.

An estimated 700,000 people in Brazil are living with hepatitis C. In 2017, in keeping with the World Health Organization (WHO) goal of eliminating HCV by 2030, the Brazilian Ministry of Health (MoH) ensured that 50,000 patients were treated. The decision to follow the most current treatment protocol available was made possible by innovative approaches to cost containment. In 2015, Brazil's National Committee for Health Technology Assessment had assessed the feasibility of incorporating sofosbuvir, a core drug of modern HCV treatment protocols, and considered which patients should receive it. Whereas the country's approach to HIV/AIDS involved offering treatment to everyone in need, the MoH adopted an incremental strategy for HCV.[1] The program started with patients with severe liver fibrosis and coinfections and expanded over time to encompass the entire patient population. Brazil has also launched a range of initiatives focused on diagnosis and prevention, as recommended by the WHO.

Extending treatment to everyone with HCV has serious financial implications, given the cost of DAAs. Since Brazil was excluded from Gilead's sofosbuvir licensing scheme, which makes discounted versions of the drug available in 91 countries, authorized generics were not available. In Brazil, the imperative to ob-

tain lower prices is augmented by patients' tendency to secure access to treatments through litigation. When preparing to purchase substantial quantities of HCV medicines to expand treatment, the MoH demanded that commercial prices be lower than international market prices.[1] In 2015, by leveraging the government's considerable purchasing power in this way, Brazil was able to secure a 90% price discount from the U.S. list price for sofosbuvir–daclatasvir.

In parallel to its negotiations with international pharmaceutical firms, Brazil has made substantial efforts to enable local production of generic versions of sofosbuvir and, more recently, daclatasvir. Since 2007, the MoH has promoted the creation of consortia involving private pharmaceutical companies and public laboratories, called productive development partnerships (PDPs), for the development of drugs considered strategically important.[2] Sofosbuvir and daclatasvir have been so designated, and multiple PDPs are working toward producing generic versions of both (one of the sofosbuvir PDPs includes Gilead, the originator company). One consortium, involving the local drug companies Microbiologica and Blanver and the federal laboratory Farmanguinhos, progressed to the point of registering a generic version of sofosbuvir with Brazil's health regulatory agency, ANVISA (Agência Nacional de Vigilância Sanitária), signaling a willingness to provide sofosbuvir at $8.50 (U.S.) per pill, one quarter of Gilead's price.[3]

In a country with severe budget constraints, reducing expenditures on HCV medicines in this way would be an important achievement that could enable the expansion of treatment programs. However, the MoH's ability to take advantage of this supply source is complicated by the intellectual property situation in Brazil.

Patent protection for sofosbuvir has been controversial in many countries, including Brazil. International and Brazilian nongovernmental organizations urged the government to deny patent protection and submitted opposition documents to the patent office (Instituto Nacional de Propriedade Industrial, or INPI) arguing, as they have elsewhere, that the science involved in the drug's development was neither new nor inventive and that despite all the medication's clinical benefits, it therefore does not deserve patent protection.[4] Pharmaceutical patents can be granted in Brazil only if they're approved by both the INPI and ANVISA. In this case, ANVISA, heeding the criticism that Gilead's product lacked novelty and inventiveness, and in light of the drug's strategic importance, refused to approve the key sofosbuvir patent.

That decision was overturned in court, however, and INPI subsequently approved a patent that was substantially narrower than what Gilead had applied for; this approval decision, in turn, was temporarily suspended by a regional court. Although the ultimate legal status of this patent in Brazil thus remains unsettled, with the local consortium claiming that its version is noninfringing, in late 2018 the MoH proceeded to purchase the less expensive product. Meanwhile, Gilead continues to press for additional patents on HCV drugs in Brazil, and to compete for MoH purchases with lower prices.

The barriers to eliminating HCV in Brazil would be heightened by patent protection, but they would not be insurmountable. The capabilities developed by the PDPs can still contribute to the Brazilian government's broader strategy for reducing prices by relying on local production. Being able to produce medicines locally, at lower cost, was crucial to reducing the prices of drugs for AIDS, diabetes, and other conditions, saving the MoH billions of dollars over the years; conversely, the inability to produce some drugs locally made price negotiations less fruitful. Even if Gilead were to obtain broad patent protection for sofosbuvir and remain the sole supplier, the existence of the local consortia and their potential to serve as alternative sources of the drug can aid the government as it engages in price negotiations. One tactic that countries may take in negotiating prices is to threaten to suspend the exclusivity rights that patents provide by issuing a "compulsory license," thereby enabling alternative sources of supply. For this to be a credible threat, patent law must allow the country to issue a compulsory license under the relevant conditions, with royalty payments to the originator company, and alternative suppliers must be available. In Brazil, thanks to changes made to the patent law in the early 2000s and to the existence of the PDPs, these conditions are satisfied. So long as the MoH is committed to HCV treatment, it has instruments available to achieve this goal.

Brazil's strategy for eliminating HCV, like its response to HIV/AIDS, shows that it is possible for resource-limited countries to make modern, high-cost health care treatments available to all. Brazil continues to provide important lessons on using industrial policy to achieve health objectives, even in the presence of pharmaceutical patents.

Disclosure forms provided by the authors are available at NEJM.org.

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# Universal Medicine Access through Lump-Sum Remuneration — Australia's Approach to Hepatitis C

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High prices can restrict access to medicines in rich and poor countries alike. Australia's approach to providing direct-acting antivirals (DAAs) for patients with hepatitis C virus (HCV) suggests that, under certain conditions, innovative approaches to payment can remove price as a barrier to access. In Australia, medicines on the national formulary are largely paid for by the government. In 2015, the authorities negotiated an agreement to spend approximately 1 billion Australian dollars (U.S.$766 million) over 5 years in exchange for an unlimited volume of DAAs for HCV from suppliers. This approach has been called the "subscription" or "Netflix" model, and the state of Louisiana announced in January 2019 that it was pursuing a similar approach for HCV. The Australian agreement is confidential, though the basic information above has been publicly reported.[1]

Is this unconventional approach a good deal for Australians? We used publicly available data, including data from Medicare Australia, to find out. Seven DAA-containing HCV products were included in Australia's formulary as of August 2017 (see table). We compiled data on government spending per drug (excluding rebates) for 24 months from March 2016, when implementation began. We estimated the number of patients treated by dividing the total expenditure by published list price per treatment course, taking into account that some drugs are prescribed jointly with others. We assumed a standard treatment course of 12 weeks, recognizing that a small proportion of patients require 8 or 16 weeks. On the basis of patient-uptake trends, we projected the total number of patients over 5 years to calculate the effective per-patient price under lump-sum remuneration. We also estimated savings over traditional per-pack pricing, assuming that traditional prices would have been 23% lower than published list prices after confidential rebates (following the methods of Iyengar et al.[2]).

We found that in the program's first 2 years, 47,122 people were treated (see graph), with pent-up demand surging in the initial 12 months and stabilizing at an average of 1586 new patients per month over year 2. (Using different methods, others have estimated that 58,280 patients initiated treatment during this period, which suggests that our estimate is conservative.[3]) If utilization rates remained at year-2 levels, a total of 104,223 patients would be treated over 5 years, yielding a per-patient drug price of AU$9,595 (U.S.$7,352). Initially, the government had estimated that only 61,500 of the 230,000 people living with HCV in Australia would be treated during the term of the agreement, for a