World Health Organization

GLOBAL REPORT ON ACCESS TO HEPATITIS C TREATMENT

FOCUS ON OVERCOMING BARRIERS

OCTOBER 2016

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ACRONYMS AND ABBREVIATIONS

ALCS	The Association against AIDS (Morocco)
API	active pharmaceutical ingredient
APRI	aspartate aminotransferase-to-platelet ratio index
ARIPO	African Regional Intellectual Property Organization
ART	antiretroviral therapy
CDC	United States Centers for Disease Control and Prevention
DAA	direct-acting antiviral (medicine)
DBS	dried blood spot
EMA	European Medicines Agency
EML	WHO Model List of Essential Medicines
EMP	WHO Department of Essential Medicines and Health Products
EOI	expression of interest
FDC	fixed-dose combination
FPP	finished pharmaceutical product
GCC	Gulf Cooperation Council
GDP	gross domestic product
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HCV	hepatitis C virus
HCC	hepatocellular carcinoma
I-MAK	Initiative for Medicines, Access & Knowledge
ITPC-MENA	International Treatment Preparedness Coalition-Middle East and North Africa
LMICs	low- and middle-income countries
MdM	Médecins du Monde
MoH	Ministry of Health
MSM	men who have sex with men
NAT	nucleic acid test/testing
NGO	nongovernmental organization
NHSO	National Health Security Office (Thailand)
OAPI	Organisation Africaine de la Propriété Intellectuelle
OECD	Organisation for Economic Co-operation and Development
OECS	Organisation of Eastern Caribbean States
PWID	people who inject drugs
RNA	ribonucleic acid
SSFFC	substandard, spurious, falsely labelled, falsified and counterfeit (medical products)
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UN	United Nations
USA	United States of America
US FDA	United States Food and Drug Administration
WTO	World Trade Organization

EXECUTIVE SUMMARY

Towards the vision of "…a world where viral hepatitis transmission is halted and everyone living with viral hepatitis has access to safe, affordable and effective prevention, care and treatment services".

– WHO Global Health Sector Strategy on Viral Hepatitis, 2016

Worldwide, approximately 80 million people are living with chronic hepatitis C virus (HCV) and millions more are newly infected each year. Annually, 700 000 people die from HCV-related complications, including cirrhosis and hepatocellular carcinoma (HCC). Despite the scope and severity of the epidemic caused by HCV, until recently, the global response to reduce the burden of this disease has been very limited and the available treatment was expensive, poorly tolerated and had low cure rates. Once infected with hepatitis C there was little chance of being cured, particularly for people living in low- or middle-income countries.

The field of HCV therapeutics has evolved rapidly: in 2013, the treatment of HCV was transformed by the introduction of a new class of medicines called direct-acting antivirals (DAAs). An 8–12-week course of these medicines can cure more than 90% of persons with chronic HCV infection. These new oral treatments offer tremendous opportunities and hope to all those who are infected. As with the upcoming new HIV treatment 20 years ago, we now have to ensure that these lifesaving treatments become accessible to all those who need them. This requires all stakeholders to work together to overcome barriers to access.

This is the first-ever global report on treatment access to hepatitis C medicines. The report provides the information that countries and health authorities need to identify the appropriate HCV treatment, and procure it at affordable prices. The report uses the experience of several pioneering countries to demonstrate how barriers to treatment access can be overcome. It also provides information on the production of new hepatitis C drugs and generic versions worldwide, including where the drugs are registered, where the drugs are patented and where not, and what opportunities countries have under the license agreements that were signed by some companies as well as current pricing of all recommended DAAs, including by generic companies all over the world.

Comparable to the early days of HIV treatment, high prices are a barrier to the scale up of HCV treatment. The new medicines were introduced at very high prices, in particular, in high-income countries. However, the pricing situation is not static and the report shows that prices in low- and certain middle-income countries are rapidly declining. Today countries can make lifesaving health services for the treatment of HCV a reality.

Despite massive challenges, some pioneering low- and middle-income countries are starting to deliver hepatitis C treatment reaching over 1 million people in 2016.

In 2015, 275 000 people living in low- and middle-income countries had received hepatitis C treatment based on the new DAAs. In Egypt, with one of the world's highest prevalence rates of hepatitis C, 170 000 people were treated with DAAs in 2015, and 500 000 more people received DAA treatment between January and September 2016. This was made possible as the price for a 28-day supply of one of the DAAs, sofosbuvir, dropped from US$ 300 in 2014 to US$ 51 in 2016. Other countries have increased efforts to address hepatitis C. For example, Brazil, India and Pakistan are expanding treatment coverage, and Georgia and Morocco have announced a plan to eliminate chronic

hepatitis infection. The steepest price decrease can be observed in countries with generic competition, which is similar to experience gained with the expansion of HIV treatment.

As treatment is scaled up, ensuring the quality of supply is of great importance. As of October 2016, the WHO programme prequalified the first DAA - daclatasvir from the innovator company. However, none of the generic DAAs that are currently on the market are approved by a stringent regulatory authority or prequalified. This is likely to change soon as the WHO Prequalification Programme has expanded to hepatitis, and a number of generic and innovator products are in the process of prequalification. This will facilitate the procurement of generic treatment by international programmes.

Prices remain high in high-income countries and those middle-income countries that do not have access to generic formulations and who fall outside of license agreements, placing a heavy burden on health systems and leading to treatment rationing. For example, in upper–middle-income countries, prices vary considerably across countries fluctuating on negotiations with innovator companies: the price of a 28-day supply of sofosbuvir ranges from US$ 2292 in Brazil up to US$ 16 368 in Romania. This report describes the various options these countries have to lower prices and make the new treatments more accessible.

Expanding HCV treatment is a critical component of a comprehensive response to hepatitis prevention and control. Countries also need to strengthen infection control. The annual number of new infections in low- and middle-income countries is still much higher than the number of people treated and cured. A major concerted effort is needed by all stakeholders to turn this trend. WHO is committed to providing assistance to countries both in infection control to halt transmission of the virus, and to provide universal access to safe, affordable, and effective care and treatment to all in line with the WHO Global Health Sector Strategy on Viral Hepatitis, 2016–2021.

Methods

To obtain information for this report, WHO conducted surveys of selected countries and pharmaceutical companies. Representatives of ministries of health were asked to complete questionnaires regarding the status of registration, importation and production of generic versions of DAAs and of HCV treatment scale up. Countries were selected to represent a range of geographical regions, income levels and hepatitis C prevalence, and to present different approaches to enhancing access to affordable DAA medicines. The selected countries were: Argentina, Brazil, Egypt, Georgia, Indonesia, Morocco, Nigeria, Pakistan, the Philippines, Romania, Rwanda, Thailand and Ukraine.

Questionnaires were also sent to four originator companies and twenty four generic DAA-producing companies regarding pricing, licensing and regulatory status. Inclusion of generic suppliers did not imply judgement about the quality of the products. Finally, representatives of selected nongovernmental organizations (NGOs) were interviewed regarding their global- and country-level activities for improving access to DAAs. Data were collected from November 2015 to March 2016. While WHO takes full responsibility for the content of this report, the data on access, registration and prices have been reproduced as provided by countries and companies. The patent data included in this report are based on the WHO patent reports on daclatasvir, sofosbuvir, ledipasvir, simeprevir, ombitasvir/paritaprevir/r and dasabuvir, as published in June 2016.

1. INTRODUCTION

Key points

- Approximately 80 million persons are estimated to have chronic HCV infection, which corresponds to a global prevalence of 1.1%. The prevalence rates are highest (≥2.5%) in West Africa, Eastern Europe and Central Asia. Annually, an estimated 700 000 persons with chronic HCV infection die untreated.
- Since 2014, new oral direct-acting antivirals (DAAs) have transformed HCV treatment, making prescribing safer and simpler. Cure rates of at least 90% have been reported after 12 weeks of treatment, regardless of HIV status, stage of liver disease or HCV treatment history.
- In April 2015, WHO included a number of the new DAAs in the WHO Model List of Essential Medicines.
- In April 2016, WHO issued updated HCV treatment guidelines that include recommendations on preferred DAA-based regimens.
- A Global Health Sector Strategy on Viral Hepatitis for 2016–2021 was adopted in May 2016 by the World Health Assembly. It includes the first-ever global targets to reduce new hepatitis infections and deaths, with a goal of eliminating viral hepatitis as a public health threat by 2030.
- Some countries have made significant efforts to promote universal access to new DAA medicines.

This chapter provides an overview of the current HCV burden, the new medicines to treat and cure HCV, the recently adopted WHO Global Health Sector Strategy on Viral Hepatitis, 2016–2021, and a snapshot of national hepatitis C elimination programmes.

1.1. HCV epidemiology

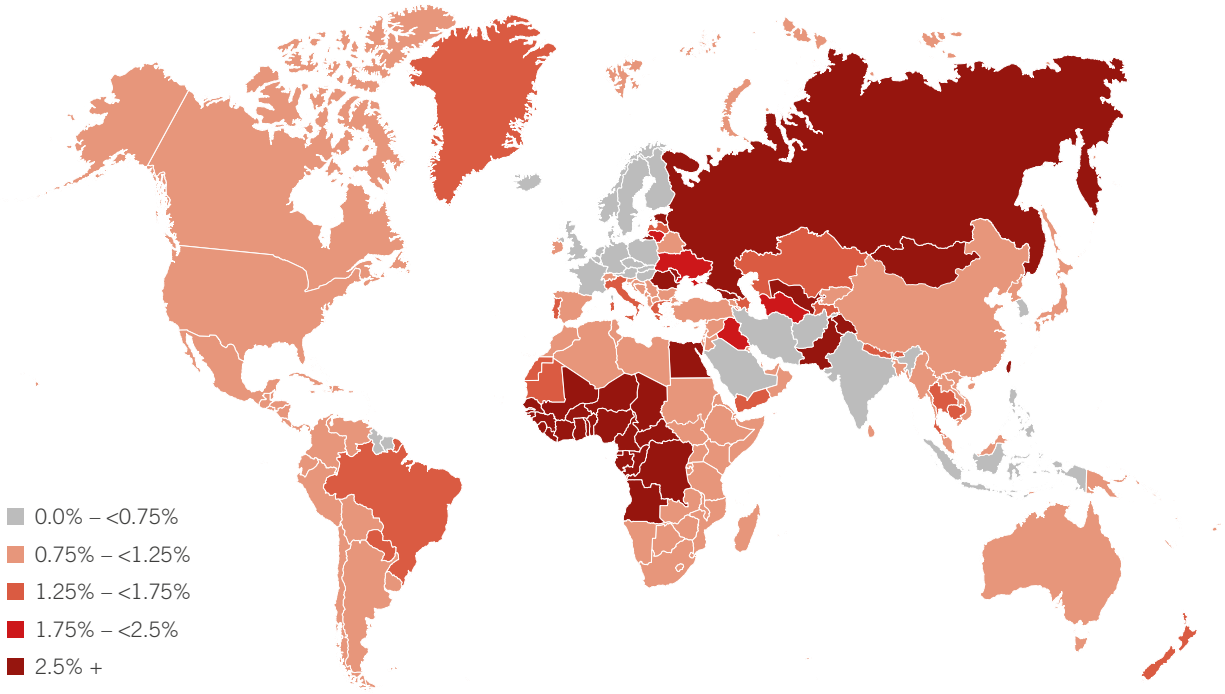
Estimates of the number of people living with hepatitis C infection vary widely. This is due in part to the fact that some authors estimate the number of people with anti-HCV antibodies, indicating exposure to the virus, while others estimate the number with HCV RNA, which indicates chronic infection *(1)*. In this report, the estimates of Gower et al. are used (Fig. 1.1), according to which there are 110 million persons with anti-HCV antibodies, indicating past or current infection, and 80 million with HCV RNA indicating current or chronic infection *(2)*. This corresponds to a global prevalence of chronic infection of 1.1%. The prevalence rates are highest (≥2.5%) in West Africa, Eastern Europe and Central Asia *(2)*. Overall, approximately 70% of persons with chronic HCV infection live in low- and middle-income countries (LMICs) *(3)*.

Hepatitis C is a small, bloodborne virus that remains infectious in dried blood for weeks *(4)*. The virus spreads via injection drug use with shared, unsterilized equipment, especially when access to harm reduction services is limited or non-existent; from medical and dental procedures in settings with inadequate infection control (including dialysis centres); tattooing with reused needles, ink and inkwells; unscreened donor blood, blood products and organs; from mother to infant; and from unprotected sex, primarily among HIV-positive men who have sex with men (MSM) *(5)*. Following exposure to the virus, infection becomes chronic in 60–80% of cases, while the remaining 20–40% of people who are infected spontaneously clear the virus *(6)*.

People who inject drugs (PWID) are the group with the highest HCV prevalence, an estimated 67%. Injections among PWID with unsterilized syringes or shared injecting equipment are the major transmission mode in high-income countries and are increasingly being reported in LMICs *(5, 7)*. The major route of transmission in LMICs is through the reuse of syringes and needles, and through substandard infection control practices in health-care settings. For example, in Egypt, an estimated 150 000 persons acquire HCV infection annually, primarily through health-care-associated transmission *(8)*.

Hepatitis C can be transmitted from mother to infant, although when and how this happens is not well understood. The risk of mother-to-infant transmission ranges from 3% to 10% *(9)*. This risk is much higher among HIV-positive mothers if they are not receiving antiretroviral therapy (ART), which lowers the risk of HCV and HIV transmission *(9, 10)*. Currently, there are no interventions to prevent transmission from mother to infant; the safety and efficacy of DAAs have not been studied during pregnancy. There are no global estimates of HCV prevalence among children. HCV is thought to progress slowly in children, but this is not always the case, and liver damage worsens with duration of infection (11– 13).

FIG. 1.1. Global prevalence of viraemic HCV (reported and extrapolated)



Source: Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology of the hepatitis C virus infection. J Hepatol. 2014; 61 (1 Suppl): S45–57 *(2)*.

Untreated HCV can cause a range of systemic health problems outside of the liver, as well as liver damage *(14)*. Once advanced liver scarring has developed, the annual incidence of cirrhosis is nearly 10% *(15)*. People with cirrhosis are at risk for liver failure and hepatocellular carcinoma (HCC); each year, these complications claim 700 000 lives *(16)*.

1.2. New medicines: moving towards elimination

Until 2014, the standard of care to treat HCV infection was 24–48 weekly injections of pegylated interferon and twice-daily ribavirin tablets. This regimen was toxic, expensive, complicated to deliver and relatively ineffective – overall cure rates were less than 50%, especially for people with cirrhosis *(17)*. Now, most people can be cured of HCV infection with the new DAAs; oral medicines that target different steps of the lifecycle of HCV. Numerous clinical trials and clinical practice have shown that DAAs are effective and better tolerated. Cure rates of at least 90% have been reported after 12 weeks of treatment, regardless of HIV status, stage of liver disease or HCV treatment history *(18)*. This has led several organizations and some countries to recommend that everyone with HCV infection should be treated with DAAs *(19)*. To date, eleven DAAs from four therapeutic classes – some formulated into fixed-dose combinations (FDCs) – have been approved by at least one stringent regulatory authority (*see* Table 1.1). In April 2016, WHO issued HCV treatment guidelines that included recommendations for DAA-based treatment for infection with all HCV genotypes (*see* section 2.2.3) *(20)*.

TABLE 1.1. Recently approved oral direct-acting antivirals for the treatment of hepatitis C

NS3/4A protease inhibitors	NS5A inhibitors	NS5B nucleotide polymerase inhibitors	NS5B non-nucleoside polymerase inhibitors
asunaprevir	daclatasvir*	sofosbuvir (nucleotide)* in fixed-dose combinations with ledipasvir or velpatasvir	dasabuvir* used with ombitasvir/ paritaprevir/r
paritaprevir/r* fixed-dose combination with ombitasvir	elbasvir fixed-dose combination with grazoprevir		
simeprevir	ledipasvir* fixed-dose combination with sofosbuvir		
grazoprevir fixed-dose combination with elbasvir	ombitasvir* fixed-dose combination with paritaprevir/r		
	velpatasvir fixed-dose combination with sofosbuvir		

r: ritonavir

* included in the WHO List of Essential Medicines; grazoprevir, elbasvir and velpatasvir were not on the market until 2016 *(21)*

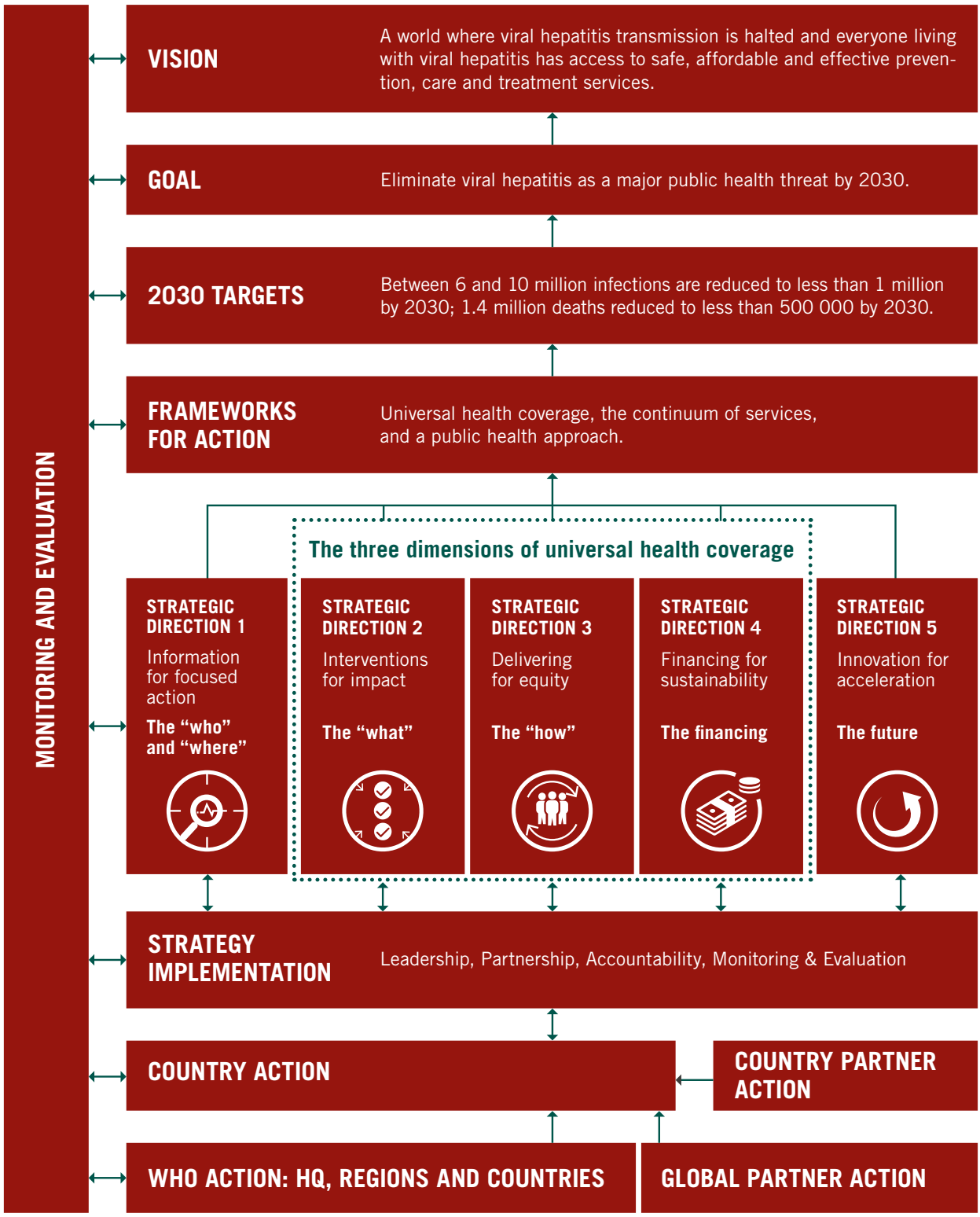
BOX 1.1. Addition of DAAs to the WHO Model List of Essential Medicines

In April 2015, the WHO Expert Committee on the Selection and Use of Essential Medicines added daclatasvir, sofosbuvir, ledipasvir, simeprevir and ombitasvir/paritaprevir/r + dasabuvir to the WHO Essential Medicines List (EML) *(21)*. By adding these new medicines, WHO is underscoring the importance of including these medicines in the national formularies of countries. Essential medicines are defined as "those that satisfy the priority health care needs of the population". According to the WHO Expert Committee on the Selection and Use of Essential Medicines, "inclusion on the EML of all DAAs proposed in the applications aims at promoting competition among available alternatives and allowing for the selection of optimal combination treatment regimens, which may or may not be existing fixed-dose combinations". The Committee also noted that WHO is working to promote the rapid introduction of prequalified generic formulations and supports countries in accessing the new DAAs at affordable prices. The selection of medicines is based on the public health relevance of the disease and a comprehensive review of available evidence on the benefits and harms of the medicines. The WHO EML is used by governments and institutions worldwide to guide the development of their essential medicines lists, to make appropriate procurement decisions and to define health-care priorities for countries.

1.3. WHO Global Health Sector Strategy on Viral Hepatitis

The availability of safe and highly effective treatment for HCV infection provides new opportunities to expand access to treatment. Lessons can be drawn from the remarkable success of HIV treatment scale up, whereby globally 17 million were receiving ART in July 2016 *(22)*. In May 2016, the WHO World Health Assembly adopted its first-ever viral hepatitis strategy that is presented schematically in Fig. 1.2 *(23)*. The strategy has an ultimate goal of eliminating hepatitis B and C as public health threats by 2030. Elimination is defined as a 90% reduction in incidence and a 65% reduction in mortality from existing levels. In addition to expanding prevention services, achieving these targets requires scaling up hepatitis treatment such that 80% of persons with chronic HBV and HCV infection are treated. Access to affordable and high-quality hepatitis medicines and diagnostics is a key element of the strategy. The strategy identifies priority actions for countries to engage in and for WHO to support countries in enhancing treatment and ensuring access to good-quality and affordable hepatitis medicines and diagnostics (*see* Box 1.2 and Box 1.3).

FIG. 1.2. Framework for the Global Health Sector Strategy on Viral Hepatitis, 2016–2021



BOX 1.2. Priority actions for WHO *(23)*

WHO is implementing priority actions for enhancing hepatitis treatment and ensuring access to good-quality and affordable medicines and diagnostics.

- WHO has produced updated treatment guidelines to promote the transition to newer, more effective medicines that have the potential to cure most persons living with hepatitis C infection in 2016 *(20)* and new guidelines for hepatitis B and C testing will be launched in November 2016.
- WHO has also produced a *Manual for the development and assessment of national viral hepatitis plans: a provisional document.* This manual provides guidance to public health professionals tasked with managing a response to viral hepatitis *(24)*.
- WHO has expanded the WHO prequalification programme to facilitate quality assurance of new DAAs, and to safeguard and expand availability of quality-assured medicines and diagnostic products.
- WHO organizes an annual consultation with pharmaceutical and diagnostic companies that produce or have a significant development pipeline of drugs and diagnostics for hepatitis, and with partner organizations to advocate for adequate manufacturing capacity of producers *(25)*.
- WHO has assessed and published the patent situation of the new DAAs to guide Member States in their procurement decisions *(26)*.
- WHO is providing Member States with technical assistance on how to expand treatment coverage.
- WHO will annually update this report on the status of access, prices, registration of hepatitis C medicines, and document the situation of the response, barriers to and opportunities for countries to increase access to DAAs.

BOX 1.3. Priority actions for countries *(23)*

Priority actions for countries to enhance treatment and ensure access to good-quality and affordable medicines

- Prioritize hepatitis treatment by including access to antiviral treatment for people with chronic viral hepatitis B and C infection as a central component of the national hepatitis strategy and plan.
- Establish national hepatitis treatment and care guidelines, plans and protocols based on the WHO hepatitis treatment and care guidelines.
- Provide quality treatment that ensures standardized care of people with chronic hepatitis infection, including appropriate disease staging, timely treatment initiation, patient and drug toxicity monitoring, and management of liver cirrhosis, HCC and liver failure.
- Address common comorbidities, including HIV infection and risk factors that may accelerate progression of liver disease, including alcohol use, and provide palliative and end-of-life care, including access to adequate analgesia.
- Strengthen the national hepatitis procurement and supply management structures and processes by ensuring that they are integrated into the broader national procurement and supply management system.
- Ensure the procurement of quality-assured hepatitis vaccines, medicines, diagnostics, condoms and other hepatitis-related commodities, including through the use of WHO prequalification.
- Plan and implement a hepatitis medicines and commodities access strategy to reduce prices of hepatitis-related commodities, including, where appropriate, through implementation of flexibilities of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), in accordance with the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property.
- Safeguard and expand availability of WHO-prequalified generic products through the expansion of licence agreements and timely registration at national level.

1.4. Examples of country action towards elimination of hepatitis

The new DAAs provide the opportunity to drastically expand treatment. Some countries have already seized this opportunity and launched national plans with the aim of providing universal treatment, covering all people with chronic HCV infection.

- In Australia, a civil society campaign led the government to broaden the criteria for eligibility for treatment. As of March 2016, the country offers universal access to HCV treatment to all persons with chronic HCV infection *(27)*. Prisoners and PWID are priority populations for expanding coverage of treatment *(28)*.

- In France, of the estimated 500 000 people living with HCV, 30 000 have been treated with DAAs as of May 2016. On France's National Hepatitis Day (25 May 2016) *(29)*, the Ministry of Health announced that it would provide universal access to HCV treatment under its national health insurance system, as of September 2016 *(30)*.

- Georgia launched a hepatitis C elimination programme in 2015. The country plans to expand treatment coverage from 5000 by end 2015 to 20 000 people per year *(31, 32)*.

- In Morocco, the Minister of Health has announced the goal of "Morocco without hepatitis C in 2030" *(33)*.

- In 2015, Portugal's Ministry of Health announced that the government would provide universal access to treatment – beginning with 13 000 people per year over a 2-year period *(34)*. Less than a year later, 5449 people had started HCV treatment under the plan. Overall, 96.3% of the 1069 persons who completed treatment were cured *(35)*.

2. STATUS OF THE RESPONSE

Key points

- Despite massive challenges, some pioneering low- and middle-income countries are starting to deliver hepatitis C treatment reaching at least 1 million people in 2016.
- Expanding access to treatment in LMICs must be a high priority to meet the goals of the new WHO Global Health Sector Strategy on Viral Hepatitis.
- WHO has produced guidance to support the health sector response, increased access to new medicines, simplified HCV diagnosis and treatment, and optimized HCV treatment and prevention services, notably to reach those populations most vulnerable to and affected by HCV infection.
- Adapting health services to reach those populations and locations most affected will be key to scaling up HCV treatment. Decentralizing service delivery and task-shifting are approaches that could be used to accelerate and expand access to HCV medicines.

This section provides an update on the number of people treated, or who were undergoing DAA-based treatment in LMICs during 2015, and reviews some of the barriers to HCV treatment access that have been documented and discussed in various forums.

2.1. Estimated number of people who received direct-acting antivirals (DAAs)

In 2015, most of the people receiving the new DAAs were living in high-income countries. According to pharmaceutical company sales' data of February 2016, 570 000 people in high-income countries had been treated with sofosbuvir-containing regimens, which is the most frequently prescribed DAA *(36, 37)*. Treatment numbers were much lower in LMICs in 2015. Based on a review of presentations at major conferences and the survey conducted by WHO for this report, an estimated 275 000 people in these countries received DAA-based treatment by the end of 2015. Of the 275 000 people treated, some 170 000 were in Egypt. An additional 500 000 people were reported to have started treatment in Egypt between January and September 2016. In September 2016, additional data reported from other countries brought the overall estimated number of people treated with DAAs in LMICs to over 1 million (*see* Box 2.1). Expanding access to treatment in LMICs must be a high priority to meet the goals of the new WHO Global Health Sector Strategy on Viral Hepatitis.

BOX 2.1. WHO estimates over 1 million treated with highly effective hepatitis C medicines[1]

- In Brazil, 7462 people were treated with DAAs by the end of 2015.
- In Egypt, 170 000 people were treated between October 2014 and end of 2015, and 500 000 more started treatment between January and September 2016.
- In Georgia, at least 5000 people were treated by the end of 2015, and 14 300 more started treatment between January and September 2016 *(31)*.
- In India, 42 000 people were treated by the end of 2015.
- In Pakistan, 47 035 people were treated from August 2014 through January 2016, and nearly 35 000 more people have started treatment since February 2016.
- In Rwanda, 120 patients started treatment through January 2016, and the country was planning to treat at least 700 patients during the course of 2016.
- In Ukraine, 320 people were treated through an Alliance for Public Health programme by the end of 2015. The programme planned to treat at least 1500 people in 2016 *(38)*.
- In countries of the WHO Western Pacific Region, an estimated 211 100 people were treated with DAAs by September 2016. These included 200 100 people in China, 5600 people in Mongolia, 4500 people in Viet Nam, 800 people in Cambodia and 200 people in Lao People's Democratic Republic.

Several other countries have introduced DAA therapy, including Argentina, Bangladesh, Côte d'Ivoire, Kenya, Nigeria, South Africa and Uganda.

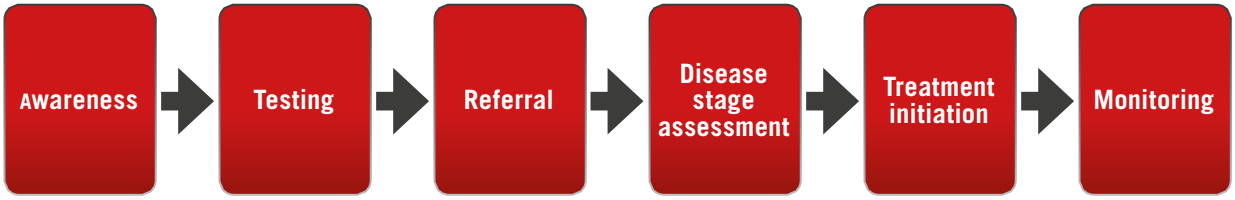
[1] Unless otherwise referenced, information on treatment numbers was obtained from country responses to the WHO country survey and from presentations at a "Joint European Association for the Study of the Liver/World Hepatitis Alliance Workshop on Regional Baseline Positions: where are we in 2016" that took place on 13 April 2016 at the International Liver Congress, Barcelona, Spain (webcast available at https://www.youtube.com/watch?v=MLeF_FgsxlU; accessed 5 August 2016).

2.2. The HCV treatment cascade: diagnosis and linkage to care

This section details the current barriers to HCV treatment related to diagnostics, and identifies possible solutions, such as dried blood spot (DBS) testing and other innovations to further simplify HCV testing. It reviews updated WHO treatment guidelines and outlines steps to facilitate HCV treatment scale up, such as task-shifting and decentralization.

While the main focus of this report is access, it is important to bear in mind the complete treatment cascade as outlined in Fig. 2.1.

FIG. 2.1. The HCV treatment cascade



2.2.1. HCV testing

There are no reliable estimates of the number of people who have been tested for hepatitis, but it is likely that less than 5% of people in LMICs with chronic HCV infection are aware that they are infected *(39)*. Lack of patient and provider awareness, poor accessibility of testing sites, inadequate resources for HCV testing services and commodities, and concerns about stigma and discrimination contribute to low diagnosis rates. In addition, HCV epidemics are heterogeneous: in some countries HCV prevalence is high in the general population, while in other countries HCV infection is concentrated in certain populations. Therefore, testing strategies must be adapted to the local context, with policy-makers developing testing policies and strategies that will reach populations with a higher prevalence (e.g. PWID) as well as those that include the majority of persons with hepatitis infection (e.g. general population in some countries).

Another challenge to the diagnosis of HCV infection is that it requires a two-step process. The first step tests for the presence of anti-HCV antibodies, and the second test, based on nucleic acid testing (NAT), is needed to distinguish those people who have spontaneously cleared the virus from those who have chronic infection. Access to NAT is limited in LMICs, as few laboratories have the capacity to perform these tests. These facilities are often available only in major cities and patients frequently bear the costs of being tested themselves. Both rapid, point-of-care diagnostics and decentralized, patient-focused testing services are needed to ensure that people are properly diagnosed and linked to care and treatment. The same interventions that strengthen linkage to, and retention in, HIV care and treatment may work for HCV. A meta-analysis of the HIV testing and care cascade in sub-Saharan Africa reported that the median rate of loss to follow up after an HIV diagnosis was 41% (range: 12–65%) *(40)*. Point-of-care CD4 cell testing in resource-limited settings has shortened the time to and increased initiation of ART for people living with HIV *(41, 42)*. Offering free HIV, HBV and HCV rapid testing can increase the number of people who know their HCV infection status. Results of rapid testing are available within minutes as compared to several days for laboratory-based serological testing. Where prevalence is high, testing programmes will have a greater yield if they focus on groups that are most affected. In a clinic in Paris for uninsured immigrants, testing for HIV, HBV and HCV using a combination rapid test increased uptake and receipt of results, from 64% to 98%, as compared with laboratory-based testing *(43)*. Another opportunity to simplify diagnosis is to test for HCV core antigen, as it is a one-step process that is simpler to conduct and less expensive than HCV NAT *(44)*.

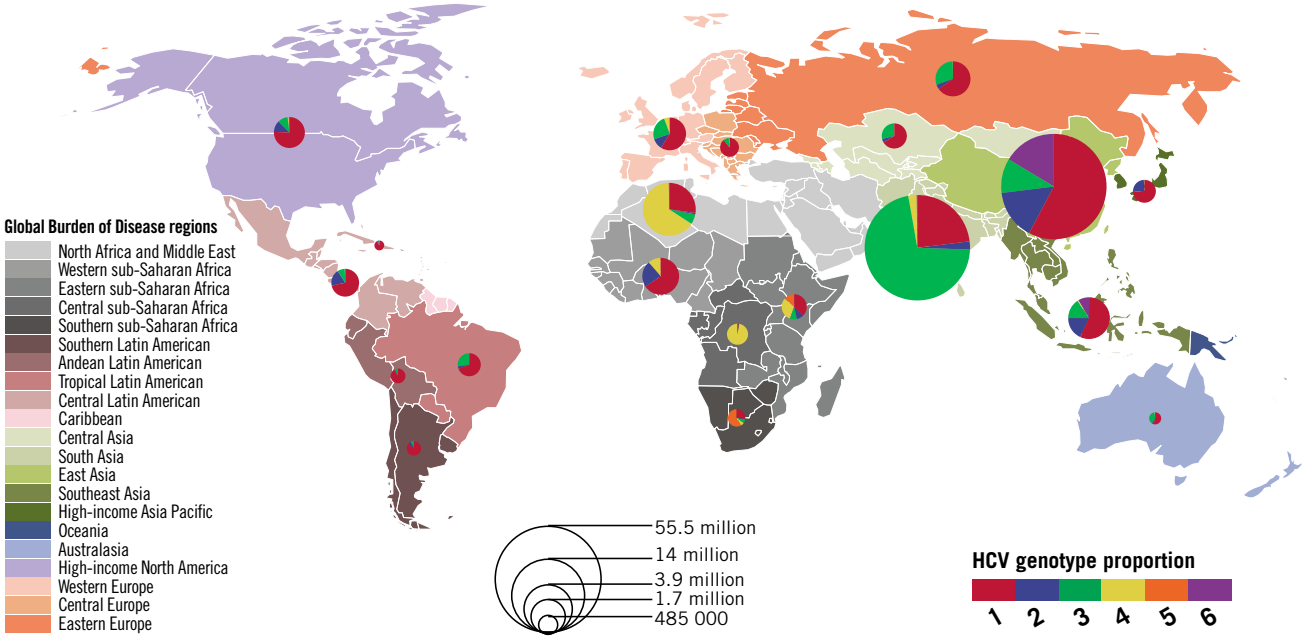
There are opportunities to expand access to HCV NAT testing through scaling up HIV viral load testing. The same platform can be used for both HBV and HCV *(45)*. The demand for HIV viral load testing in LMICs is projected to reach 15–30 million by 2018 (from 7 million in 2013).

Using DBS testing for HCV screening and diagnostic tests could increase the simplicity of and access to these tests. The 2016 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend DBS testing to facilitate HIV viral load testing in resource-limited settings *(46)*. In high-income countries, using DBS has facilitated and increased uptake of HCV testing in prisons and drug treatment centres among people with veins that are difficult to access; it has also been effective in resource-limited settings *(47, 48)*.

2.2.2. Pre-treatment assessment: HCV genotyping and liver disease staging

There are six major HCV genotypes. HCV genotype 1 infection is the most common; however, taken together, genotypes 2–6 make up more than half of all HCV infections (Fig. 2.2) *(49)*.

FIG. 2.2. Global distribution of HCV genotypes



Source: Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61(1):77–87 *(49)*.

Currently, the type and duration of HCV treatment varies according to both genotype and cirrhosis status, as reflected in the 2016 WHO *Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection (20)*. Therefore, genotype testing is still necessary prior to treatment initiation. This test is expensive and is not widely available in LMICs because it requires sophisticated equipment and specially trained laboratory staff.

Staging of liver disease to identify people with pre-cirrhosis or cirrhosis is an important pre-treatment assessment, for two reasons: to prioritize people with advanced liver disease where access to HCV treatment is limited, and to determine the optimal regimen, duration and monitoring schedule for HCV treatment.

Liver biopsy has been the "gold standard" for staging liver disease in high-income countries, although it is expensive, invasive and unpopular with patients. It is not feasible in resource-limited settings. Recently, less invasive methods such as transient elastography and blood tests that measure direct markers of liver fibrosis have been used together instead of biopsy, and are recommended by treatment guidelines from the USA and the European Union *(50, 51)*. In resource-limited settings where these less invasive methods may be unavailable or unaffordable, WHO recommends a combination of routine blood tests (aspartate aminotransferase-to-platelet ratio index [APRI] or FIB-4) to assess liver fibrosis *(20)*.

2.2.3. Treatment guidelines

Recognizing the global burden of hepatitis and the promise of DAAs, in 2014, WHO released the first-ever guidelines on HCV screening, care and treatment intended for LMICs. The standard of care for HCV is changing so rapidly that an updated version of the WHO Guidelines for the screening, care and treatment was issued only two years later – in April 2016. The guidelines will require updating with the advent of pangenotypic DAA regimens that allow a simplified public health approach to HCV treatment. WHO is planning to update the treatment recommendations in 2017.

For the time being, there are three WHO-recommended, preferred regimens for people without cirrhosis (sofosbuvir, with daclatasvir or ledipasvir or ribavirin) (Table 2.1). For people with cirrhosis, the same DAAs are used but the duration may differ and ribavirin may be added *(20)*.

The WHO guidelines also include recommendations for alternative DAA regimens (Table 2.2). These regimens were not considered as preferred for various reasons (for example, because of limited data, pill burden, adverse events, drug interactions, effectiveness limited to certain genotypes, safety in people with decompensated cirrhosis) *(20)*.

None of the DAAs are approved for use among children; thus, the standard of care for hepatitis C infection among children remains pegylated interferon and ribavirin. Clinical trials evaluating the efficacy and safety of DAAs in children are under way.

TABLE 2.1. Summary of recommended preferred treatment regimens with treatment durations*

Persons without cirrhosis

Genotype	Daclatasvir/sofosbuvir	Ledipasvir/sofosbuvir	Sofosbuvir/ribavirin
Genotype 1	12 weeks	12 weeks[a]	
Genotype 2			12 weeks
Genotype 3	12 weeks		24 weeks
Genotype 4	12 weeks	12 weeks	
Genotype 5		12 weeks	
Genotype 6		12 weeks	

Persons with cirrhosis

Genotype	Daclatasvir/sofosbuvir	Daclatasvir/sofosbuvir/ribavirin	Ledipasvir/sofosbuvir	Ledipasvir/sofosbuvir/ribavirin	Sofosbuvir/ribavirin
Genotype 1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 2					16 weeks
Genotype 3		24 weeks			
Genotype 4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 5			24 weeks	12 weeks[b]	
Genotype 6			24 weeks	12 weeks[b]	

* Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) *(50)* and European Association for the Study of the Liver (EASL) *(51)*.

[a] Treatment may be shortened to 8 weeks in treatment-naive persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution.

[b] If platelet count <75 x 10^3/μL, then 24 weeks' treatment with ribavirin should be given.

TABLE 2.2. Summary of recommended alternative regimens with treatment durations*

Persons without cirrhosis

Genotype	Simeprevir/sofosbuvir	Daclatasvir/sofosbuvir	Ombitasvir/paritaprevir/ritonavir/dasabuvir	Ombitasvir/paritaprevir/ritonavir/ribavirin	Sofosbuvir/pegylated interferon /ribavirin
Genotype 1	12 weeks[a]		12 weeks[b]		
Genotype 2		12 weeks			
Genotype 3					
Genotype 4	12 weeks			12 weeks	
Genotype 5					12 weeks
Genotype 6					12 weeks

* Treatment durations are adapted from the 2015 AASLD and EASL guidelines *(50, 51)*.

[a] If genotype 1a-infected patient is positive for the Q80K variant, a simeprevir/sofosbuvir regimen should not be chosen.

[b] For genotype 1a-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin; for genotype 1b-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir.

Persons with cirrhosis

Genotype	Can be prescribed to persons with compensated or decompensated cirrhosis	These regimens should be prescribed only to persons with compensated cirrhosis because they can cause liver failure and death when prescribed to persons with decompensated cirrhosis. Therefore, they should be used only in settings where specialized care is available and where the degree of cirrhosis (compensated vs decompensated) can accurately be assessed.				
	Daclatasvir/ sofosbuvir	Simeprevir/ sofosbuvir	Simeprevir/ sofosbuvir/ribavirin	Ombitasvir/ paritaprevir/ ritonavir/dasabuvir	Ombitasvir/ paritaprevir/ ritonavir/ribavirin	Sofosbuvir/ pegylated interferon/ribavirin
Genotype 1		24 weeks[a]	12 weeks[a]	24 weeks[b]		
Genotype 2	12 weeks					
Genotype 3						12 weeks
Genotype 4		24 weeks	12 weeks		24 weeks	
Genotype 5						12 weeks
Genotype 6						12 weeks

* Treatment durations are adapted from the 2015 AASLD and EASL guidelines *(50, 51)*.

[a] If genotype 1a-infected patient is positive for the Q80K variant, a simeprevir/sofosbuvir regimen should not be chosen.

[b] For genotype 1a-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin for 24 weeks; for genotype 1b-infected patients, treat with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin for 12 weeks.

2.2.4. HCV treatment delivery

The safety, ease of use and high cure rates associated with DAAs allow a paradigm change from treating only those persons with advanced liver damage to treating all those with HCV infection. In fact, WHO's Global Health Sector Strategy on Viral Hepatitis includes a target to treat 80% of all persons with chronic HBV and HCV infection who need treatment. For this to happen, testing and treatment services will need to be dramatically expanded and a number of obstacles will need to be overcome. Some of these apply to low-, middle- and high-income countries, such as limited awareness, low diagnosis rates, lack of decentralized care and treatment, stigma and discrimination, while others – such as high prices – affect primarily upper–middle-income and high-income countries.

Treatment services need to be planned and implemented such that equitable access to quality treatment services is assured for all those who need them. This is the responsibility of national governments, who should plan treatment services in the context of a broader national hepatitis plan that includes comprehensive prevention services. Such planning should be based on reliable data concerning the numbers and geographical distribution of people with HCV infection to help ensure the availability of services where they are most needed.

Expanding access to HCV treatment will require new approaches to service delivery. To ensure accessibility, treatment services will need to be decentralized to lower levels of the health-care

system and be delivered by non-specialist providers. Task-shifting to nurses and community health workers has been successful for delivery of other treatments, including lifelong HIV treatment, and is recommended by WHO *(46)*. The same approach is likely to be effective for hepatitis C treatment, especially because of its short duration, limited monitoring requirements and safe, tolerable once-daily regimens. Linking hepatitis treatment services with other components of the health system is important to help assure that these services are accessible. Opportunities for service linkage include locations where services are provided for reproductive and sexual health, harm reduction, drug and alcohol use disorders, and noncommunicable diseases.

Technology can support non-specialist care and treatment. In rural areas, telemedicine is used to increase the capacity to deliver HCV treatment, and there are now a range of HCV treatment smart-phone applications to support providers and patients *(52)*. In HIV, task-shifting and mobile or home-based testing initiatives have improved linkage to care in LMICs, and are likely to do the same for HCV *(53)*.

Another challenge is to make treatment services accessible to specific populations with high HCV prevalence and variable access to health care, such as PWID, prisoners, people living with HCV/HIV coinfection, migrants and MSM. It is important to make special efforts so that treatment services are accessible to these groups. PWID, in particular, face numerous barriers to accessing HCV treatment; some can be surmounted by adopting enabling policies and guidelines, and decentralizing care. Access to harm reduction programmes and services is inadequate, and people face a range of barriers that complicate access to HCV treatment, including stigma and discrimination. Specific strategies to engage and retain PWID in HCV treatment need to be included in national treatment plans. Data from clinical trials and community-based programmes that deliver tailored services for PWID show that treatment adherence and cure rates can be high *(54–56)*. Involving these populations in the development, implementation and oversight of HCV services is essential to address stigma, and increase access to diagnostics, care and treatment.

2.2.5. DAA treatment in the present and the future

For now, sofosbuvir is the backbone of all multi- and pangenotypic regimens. Although data on sofosbuvir/daclatasvir in infection with genotypes 4, 5 and 6 are limited, this combination appears to be safe and highly effective for all HCV genotypes *(57)*.

Having a single preferred first-line regimen that is effective in all genotypes (referred to as a pangenotypic regimen) will facilitate treatment expansion. In June 2016, a pangenotypic, fixed-duration regimen (sofosbuvir/velpatasvir) was approved by the United States Food and Drug Administration (US FDA) *(58)*. It was not included in the 2016 WHO guidelines as it had not been approved at the time the recommendations were formulated. Other pangenotypic FDCs of two or three DAA classes are in the late stages of development. Pangenotypic DAA regimens are optimal for resource-limited settings, as they simplify diagnosis (i.e. no need for genotyping), assessment of pretreatment fibrosis, procurement and delivery, and reduce prescribing and dispensing errors.

3. ACCESSING AFFORDABLE DAA MEDICINES IN DIFFERENT SETTINGS

Key points

- Access to DAAs must be scaled up if treatment is to have an impact on reducing HCV mortality and preventing new infections.
- Increasing generic competition is beginning to have an impact on the prices of DAAs, which are becoming more affordable in low- and most lower–middle-income countries. Actual production costs are low, offering opportunities for low-cost, large-scale generic production, but high-income and upper–middle-income countries, in particular, are facing high prices that have led to rationing of treatment.
- Different measures have been used to increase affordability and improve access to DAAs, including optimized procurement, voluntary licenses, local production and patent oppositions.
- Expanding registration of the new DAAs in LMICs is essential for expanding access.
- The WHO prequalification process can contribute to ensuring the quality of generics; WHO also has a surveillance and monitoring system to collect and share data on falsified medicines.
- This report provides strategic information on registration status, the patent situation and pricing to facilitate access to the new DAAs.

3.1. Price developments

One of the main barriers in middle- and high-income countries is the lack of funding and the high prices of the new medicines. Initial prices of DAAs in high-income countries were extremely high, and have continued to remain high in many countries. For example, sofosbuvir, which was introduced in late 2013, was priced at US$ 1000 per pill in the USA and sofosbuvir/ledipasvir at US$ 1125 per pill. This even triggered the attention of the US Congress that investigated the pricing of sofosbuvir *(59)*.

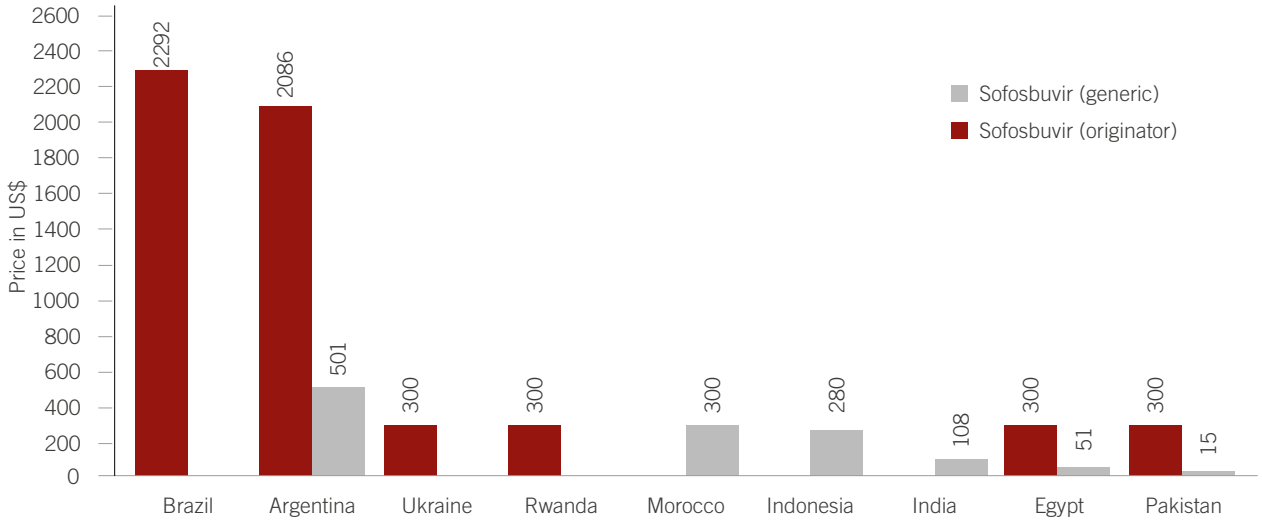
High prices and limited funding can force countries to ration or only gradually upscale HCV treatment. Some examples are given below.

- In Brazil, people with no or mild fibrosis are not eligible for treatment.
- Switzerland initially rationed access to treatment, excluding patients with mild or no liver damage because of high prices, and expanded access only after the country negotiated slight price reductions from originator companies *(60)*.
- In the USA, patients in California and Washington State filed lawsuits against a private insurance company and private payers for restricting access to HCV treatment *(61, 62)*.

Many middle-income countries have a high disease burden of hepatitis C. Affordable prices are a prerequisite for these countries to be able to increase treatment coverage. Actual production costs are low, offering opportunities for low-cost, large-scale generic production, as for HIV treatment. In January 2015, 1 kg of the active pharmaceutical ingredient (API) for sofosbuvir cost between US$ 8000 and US$ 9000: by February 2016, the price had dropped to between US$ 1500 and US$ 3000. It was estimated that sofosbuvir, the backbone of most HCV treatment regimens, could be mass-produced for just over US$ 1 per pill which could bring the cost for mass production of generic sofosbuvir to US$ 29 for a 28-day supply *(63)*. With daclatasvir, the price of API has dropped from just under US$ 2000 per kg to approximately US$ 1500 per kg, making it possible to bring down the production cost to an estimated US$ 5.5 for a 28-day supply *(63)*.

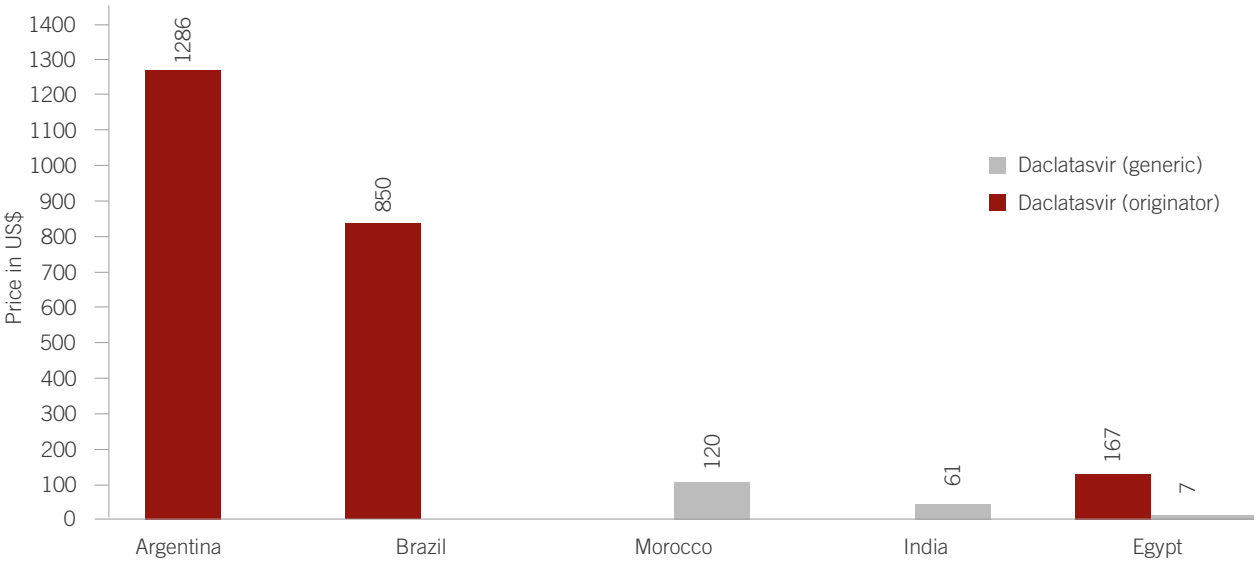
Those countries that are able to procure generic DAAs can benefit from lower prices as, with increasing competition, the prices of generic DAAs are dropping rapidly, as shown in Fig. 3.1 and 3.2. Generic production can take place in those countries where relevant patents have not been filed or granted or where patents are still under examination (*see* under section 3.5). In Egypt, where sofosbuvir is not patented, it is available for US$ 51 for a 28-day supply from local producers. Generic DAAs are also produced under license agreements (*see* under section 3.5.2). Prices for DAAs from these licensed generic producers are also falling rapidly. In January 2016, the lowest price reported for a 28-day supply of a generic FDC of sofosbuvir/ledipasvir by Indian licensees of the originator company for the local Indian market was US$ 205; by April 2016, it dropped to US$ 169 *(64)*. The lowest price reported for a 28-day supply of sofosbuvir in January 2016 from a local generic producer was US$ 15 in Pakistan (*see* under Chapter 5. Drug profiles). For daclatasvir, the price for a 28-day supply of a generic formulation dropped to US$ 120 in Morocco, US$ 61 in India and down to US$ 7 in Egypt.

FIG. 3.1. The price of a 28-day supply of sofosbuvir in different countries



Source: Data obtained from WHO survey on DAA pricing in selected countries, 2016

FIG. 3.2. The price of a 28-day supply of daclatasvir in different countries



Source: Data obtained from WHO survey on DAA pricing in selected countries, 2016

3.2. Price transparency, price negotiation and price control

To enable countries to successfully negotiate more affordable prices, greater market transparency is needed. This report endeavours to provide comprehensive information on the current pricing situation, the sources from which generic products are currently available, and which countries may procure generic products either because they are not under patent or because they are included in the relevant license agreements (*see* for detailed information the drug profiles in Chapter 5).

The information provided should enable countries to engage in more strategic procurement where legally they may procure the new DAAs from various sources, achieving better deals through competitive bidding processes.

Countries that are not able to procure from generic sources have to engage in price negotiations unless they use TRIPS flexibilities. Successful price negotiations require market intelligence, in particular, on what other countries and buyers are paying. The pricing information provided in this report thus should assist buyers to better assess the market prices and fix goals in price negotiations.

Many high-income countries provide for some sort of mechanism to control and fix prices in the medical sector. While it is beyond the scope of this report to assess the performance of the various systems implemented, Box 3.1 provides an overview on the current pricing levels in high-income countries.

Many pharmaceutical companies have different price structures and models. Some companies adjust their policies on a country-by-country basis while others have predefined policies for groups of countries that can be based on a variety of criteria such as gross domestic product (GDP) and disease burden. This kind of differential pricing policy can also contribute to savings, in particular, for countries that are in the lowest tier. The originator company, for example, offers sofosbuvir at US$ 300/28-day supply and sofosbuvir/ledipasvir at US$ 400/28-day supply in the 101 countries that are included in its license agreement. Lessons learnt from the HIV field, however, show that while differential pricing can result in lower prices of medicines, generic competition is more effective in driving down prices *(65)*.

BOX 3.1. Prices, costs and affordability of new medicines for hepatitis C treatment in high-income countries

Research carried out by WHO and the Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies at the Austrian Public Health Institute systematically compared the price and affordability of sofosbuvir and ledipasvir/sofosbuvir across 26 member countries of the Organisation for Economic Co-operation and Development (OECD) and four LMICs to assess affordability for health systems and patients.

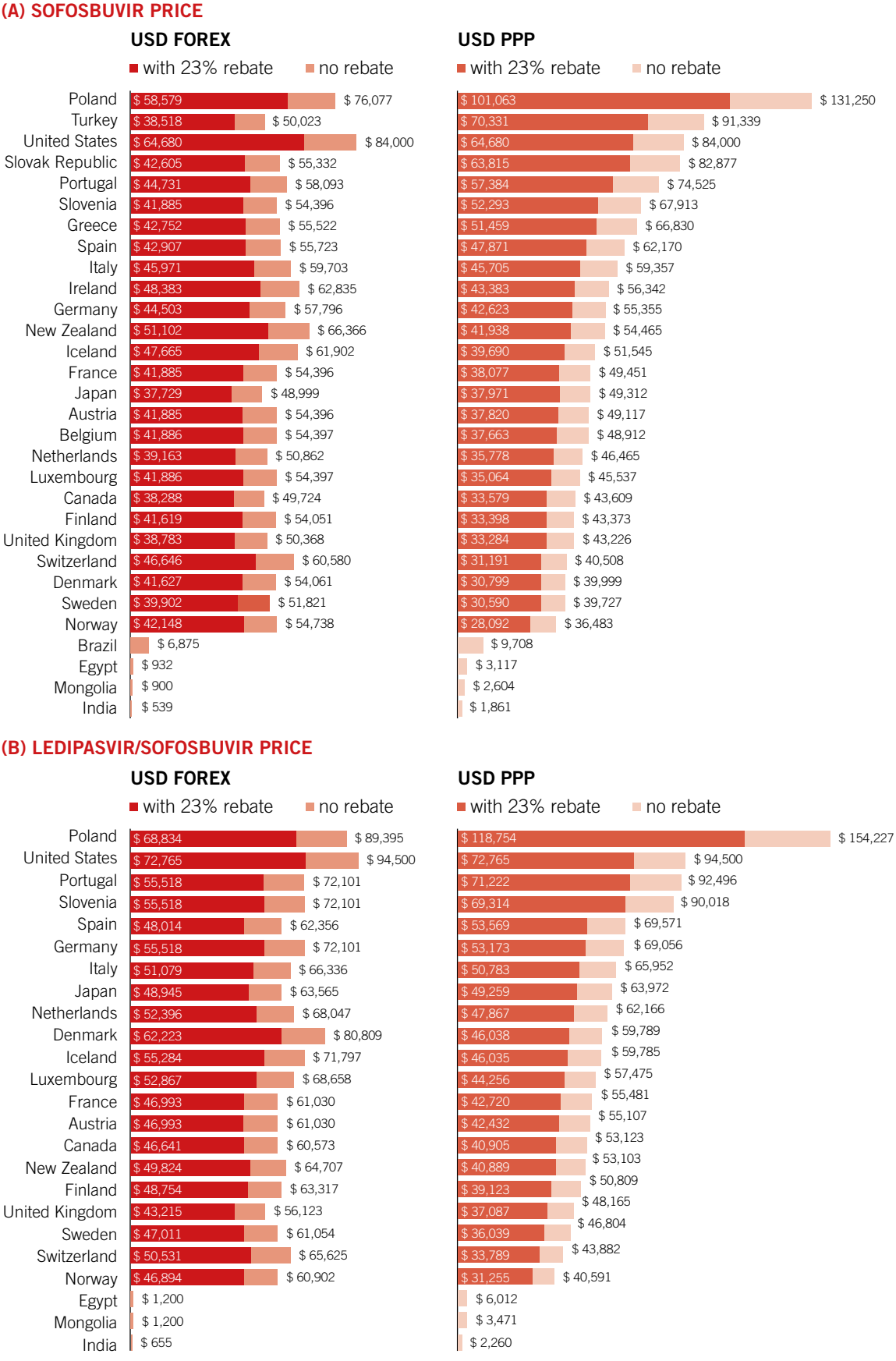
The total cost of treating all patients with hepatitis C, adjusted for currency differences and national wealth, ranged from 10.5% (the Netherlands) to 190.5% (Poland) of the current annual cost for all medicines among the OECD countries studied. In five OECD countries where prices are high and the burden of disease is high, the total cost of treating all infected patients would be more than the cost of all other medicines put together. If a patient had to pay for the treatment out of pocket, the total cost of a full course of sofosbuvir alone would be equivalent to one year or more of average earnings for individuals in 12 of the 30 countries analysed.

The prices of the medicines for hepatitis C treatment vary considerably across countries, particularly when adjusted for national wealth (Fig. 3.3). Poorer countries may be paying higher adjusted prices than richer countries.

Paying for sofosbuvir and ledipasvir/sofosbuvir in national health systems would consume large proportions of their total pharmaceutical budget. The potential total cost of treatment presents a financial and ethical dilemma for payers and physicians. Some national health systems have therefore restricted access to these medicines to small groups of patients, despite the fact that almost all patients with chronic hepatitis C infection are likely to benefit from treatment with these medicines. For countries to increase investment and minimize the burden of hepatitis C, governments and industry stakeholders will need to jointly develop and implement fairer pricing frameworks that lead to lower and more affordable prices.

For further information on the methodology and results of the study, *see* reference *(66)*.

FIG. 3.3. Prices of medicines for hepatitis C in 30 countries



PPP: purchasing power parity

Source: Iyengar S, Tay-Teo K, Vogler S, Beyer P, Wiktor S, de Joncheere K, et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. PLoS Med. 2016; 13(5):e1002032. doi:10.1371/journal.pmed.1002032 *(66)*.

3.3. International quality assurance standards

While price reductions offer great opportunities for scaling up treatment services, assessing the quality of generic medicines remains of key importance. To be eligible for international donor programmes, any product needs to comply with international quality assurance standards and thus needs to be either prequalified by WHO or authorized by a stringent regulatory authority or otherwise proven to be in line with international standards. As of July 2016, none of the generic DAAs produced by companies working within or outside the license agreements has been approved by a stringent regulatory authority or prequalified. However, the WHO Prequalification Programme has expanded to include the new DAAs, and a number of products are in the process of prequalification. In mid-October 2016, the Programme prequalified the first DAA – daclatasvir 30 mg and 60 mg, from the originator company. Several generics are in the pipeline.

The WHO Prequalification Programme was established in 2001 to assist the United Nations and other international procurers to identify quality-assured medicinal products for bulk purchase and distribution to recipient countries. It covers both finished pharmaceutical products (FPPs) and APIs. The prequalification requirements are similar to those of other stringent regulatory organizations such as the European Medicines Agency (EMA) or US FDA. This includes submission of evidence of safety/efficacy (for a generic, this means a bioequivalence study comparing the product against an acceptable comparator product, usually the innovator), as well as evidence that the API and FPP can be manufactured and controlled to consistently meet internationally accepted quality standards, and remain stable for a reasonable amount of time.

By July 2016, the Prequalification of Medicines Programme had received seven FPP applications for hepatitis C medicines and four sofosbuvir API applications, either to support the mentioned FPP dossiers, or to support prequalification of the sofosbuvir API itself. Five of the seven FPP applications are for sofosbuvir tablets, while the other two were for daclatasvir 30 mg and 60 mg tablets from the innovator company. All the FPPs and API applications have been screened and are now under full assessment.

The median time taken by WHO from submission of a dossier by a manufacturer to prequalification (full assessment) is approximately 200 days. Depending on a manufacturer's experience and own priorities, 18 months or more may be required for a manufacturer to complete the requirements for prequalification, including demonstration of bioequivalence. For products already approved by a stringent regulatory authority, WHO prequalification can rely on such approval. In such cases, the total time to prequalification is generally 1–3 months.

3.4. Registration of DAAs in countries

Registration fulfils an important public health role in assuring that a medicine is safe, efficacious and of good quality. Therefore, medicines cannot be sold in a given country until they have been approved by the relevant national or regional regulatory agency. Given that manufacturers have to seek authorization in all countries where they plan to market their product, they apply a step-wise approach, prioritizing countries using different criteria such as market size, expected revenue and disease burden. This means that filing for market authorization in certain countries will be delayed. In addition, the registration process takes time, in particular, where additional local clinical trials are required or authorities are understaffed. Thus, in many countries, the new DAAs are still not authorized for the market and consequently not available (*see* the data on each medicine in Chapter 5). In some cases, the requirement for local trials was waived. For example, in India, community-

based advocates successfully petitioned – along with generics companies – to obtain waivers for sofosbuvir and daclatasvir *(67, 68)*. As a result, these DAAs were registered and became available much sooner than if in-country clinical trials needed to be conducted.

The lack of registration of the originator products also hampers the availability of generic alternatives, including in those countries that have voluntary license agreements. In general, when an originator company registers its product, this facilitates the registration of generic versions, as regulatory authorities and generics producers can refer to the dossier and market authorization held by the originator (unless data exclusivity rules prevent generic manufacturers from referring to the data submitted by the originator company). It is also important that the originator companies register not only their FDCs, but also the individual components to allow new generic combinations, for example, of sofosbuvir and daclatasvir, to enter the market *(57, 69, 70)*.

In the absence of registration of the originator products, countries can rely on prequalification and referral to other stringent regulatory approvals to speed up registration of generic DAAs. The fact that the license agreement on daclatasvir requires the generic manufacturers to seek prequalification or approval by a stringent regulatory authority should facilitate their registration and uptake.

BOX 3.2. Falsified hepatitis C products in South-East Asia

WHO has developed a surveillance and monitoring system designed to significantly improve the quantity and quality of data on substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products. As of March 2016, over 1050 products had been reported to the WHO database. (*See* http://www.who.int/medicines/publications/drugalerts/en/.)

In February 2016, WHO was informed by a local nongovernmental organization (NGO) working in Myanmar about falsified versions of two of the new DAAs included in the WHO EML. It is almost impossible, even for a trained health-care practitioner, to identify these products as false based solely on visual inspection. The manufacturer indicated on the label confirmed to WHO that it does not manufacture these products, which have therefore been confirmed to be false. WHO issued an international drug alert about these products and called for detailed laboratory analysis to better assess the risk to public health. Samples are still pending laboratory testing. These products are thought to still be in circulation.

3.5. Overcoming patent-related barriers to access

A patent allows the patent holder to prohibit others from commercially using the invention and, for example, to manufacture, sell, export or import the patented product. Thus, whether a country can procure generic medicines depends on whether patents are filed and granted or not and, if patents are filed or granted, whether the country in question is included in the territory of the respective voluntary license agreements. A country can also issue a compulsory license to access generic treatment.

Numerous patents have been filed in relation to the new DAAs. It is important for procurement agencies to be aware of the patent situation in their country when they engage in procurement or negotiate pricing agreements. WHO has published patent reports on daclatasvir, sofosbuvir, ledipasvir, simeprevir, ombitasvir/paritaprevir/r and dasabuvir, and updates them regularly *(26)*. These reports provide an indication of what kind of patents have been filed on the different medicines, to what extent they are relevant and where these patents have been filed. *See* the summary in Table 3.1. UNITAID has published additional reports covering elbasvir, grazoprevir and velpatasvir in July 2015 *(71–73)*.

Patents can be granted for products and manufacturing processes if all of the patentability criteria are met. In the case of chemical molecules, often a number of patents are filed reflecting different steps in the drug development and manufacturing process. Product patents in the area of medicines usually cover the chemical molecule or active ingredient (referred to as primary patents) and, where considered patentable, variations of an existing chemical molecule, combinations, manufacturing processes, methods of treatment and formulations (referred to as secondary patents). For more information, *see* the WHO Patent reports *(26)*.

Patents are territorial rights and thus are valid only for the country or region where they are applied for and granted. The patent applicant may decide to apply for and pursue patent protection in one country but not in another. For example, the primary patents for sofosbuvir were not filed in Morocco and Georgia. Definition of patentability criteria and the practice of patent offices can vary from country to country. Some countries (including Argentina, India and the Philippines) interpret patentability criteria more narrowly than others or have excluded certain pharmaceutical inventions from patentability. Thus, the same patent application may be granted in one country and rejected in another *(74–76)*.

3.5.1. Patent oppositions

With respect to the new DAAs, a number of NGOs as well as generic companies have filed patent oppositions in different jurisdictions. Many patent laws allow interested third parties to file such oppositions against a patent before and/or after it has been granted (pre- or post-grant opposition). Such procedures help ensure that only those patents that meet all patentability criteria are granted and upheld. Based on the oppositions filed and as a result of the patent examination process, a number of patent applications for DAAs have been refused in different countries. For details, *see* http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)*.

3.5.2. Voluntary license agreements

Many LMICs can procure generic daclatasvir, sofosbuvir and ledipasvir from manufacturers that have entered into a license agreement with the originator companies. Under such license agreements, a patent holder permits a generic company to manufacture and sell the patented medicine in a defined number of countries. In return, the patent holder may receive royalty payments. The originator company of sofosbuvir has signed license agreements with 11 Indian generic manufacturers, allowing them to sell and market sofosbuvir, ledipasvir and velpatasvir in 101 countries *(77)*. The originator company of daclatasvir has signed an agreement with the Medicines Patent Pool, which enables sublicensing to multiple generic manufacturers and marketing in 112 countries *(78)*. All countries included in these agreements (*see* Table 3.2) can procure generic products from the licensees. As the Indian companies that are generic licensees for sofosbuvir have started to manufacture and sell sofosbuvir, prices have fallen considerably (*see* Chapter 5. Drug profiles). To allow a competitive market, license agreements need to cover a broad territory, be non-exclusive, and include a number of generics-producing companies. They should be made public and ideally be negotiated through the Medicines Patent Pool to ensure transparency, and include pro-competitive, public health-friendly terms and conditions.

Both licenses allow for the marketing of generic formulations of DAAs for a large number of countries (including more than two thirds of all middle-income countries for daclatasvir). However, these agreements do not include a number of middle-income countries with large populations and disease burden, notably Thailand (0.9 million), Brazil (1.9 million) and China, the latter having the largest number of people living with HCV infection (8.9 million) *(2)* (and *see* Chapter 5. Drug profiles).

TABLE 3.1. Summary of patent information of selected direct-acting antivirals in certain low- and middle-income countries

	simeprevir		sofosbuvir		ledipasvir		daclatasvir		paritaprevir		ombitasvir		dasabuvir	
Argentina	G	G	F	F	F	G	F	F	F	F	F	F	G	G
ARIPO	G	F	--	G	F	F	--	--	•	•	•	•	•	•
Australia	G	G	G	G	G	F	G	G	G	G	G	G	G	G
Brazil	F	F	F	F	F	F	F	F	F	•	•	F	•	•
Chile	F	G	G	F	F	F	G	G	•	F	F	F	F	F
China	G	G	G	F*	G	F	G	G	G	G	G	G	G	F
Colombia	G	G	G	G*	G	G	G	G	G	F	F	G	F	F
Costa Rica	F	F*	--	F	--	F	--	--	F	•	•	F	F	F
EAPO	G	G	--	F	G	F	G	G	G	F	G	F	•	F
EPO	G	G	G	G	G	F	G	G	G	G	G	G	G	F
Ecuador	F	F	--	F	F	F	--	--	F	F	F	F	F	F
Egypt	F	F	--	F*	--	F	F*	F	•	•	F	F	F	F
Ethiopia	--	--	--	--	--	--	--	--	•	•	•	•	•	•
GCC	F	F	--	F	--	F	F	G	•	•	F	F	F	•
Georgia	--	--	--	--	--	--	--	--	•	•	•	•	•	•
Indonesia	F	--	G	F	F	F	--	F	•	F	•	F	F	F
India	F	G	G	F	F	F	F	F	F	F	F	F	F	F
Iran (Islamic Republic of)	--	--	--	--	--	--	--	--	•	•	•	•	•	•
Israel	G	G	G	G	G	F	G	G	G	F	G	F	F	F
Japan	G	G	G	G	G	G	G	G	G	G	G	G	G	G
Jordan	F	F	--	--	--	--	--	--	•	•	•	•	•	•
Lebanon	•	•	•	•	•	•	G	--	•	•	•	•	•	•
Malaysia	G	F	G	F	--	F	--	F	F	F	F	F	F	F
Mexico	G	G	G	G	G	F	G	G	G	F	F	G	F	F
Morocco	--	--	--	G	--	F	--	--	•	•	•	•	•	•
New Zealand	G	G	G	G	G	G	G	G	G	G	G	G	G	G
Nigeria	G	--	--	--	--	--	--	--	•	•	•	•	•	•
OAPI	G	--	--	G	G	F	--	--	•	•	•	•	•	•
Pakistan	F	F	--	F	F	F	--	--	•	•	•	F	F	•
Peru	G	--	--	F	G	F	G	G	G	F	F	F	F	F
Philippines	G	G	G	F	--	F	--	F	•	G	G	G	F	F
Russia	G	G	G	G	--	F	G	G	--	G	•	•	G	•
South Africa	G	G	G	G	G	F	G	G	G	G	G	G	G	G
Republic of Korea	G	G	G	G	G	F	G	G	G	G	F	G	G	F
Singapore	G	G	G	G	G	F	G	G	G	G	F	F	G	G
Thailand	F	F	F	F	F	F	F	F	--	F	•	F	F	•
Tunisia	--	--	--	--	--	--	--	--	•	•	•	•	•	•
Ukraine	G	G	--	F	G	F	--	--	G	•	G	G	•	F
Uruguay	F	--	--	F	F	F	--	F	--	F	F	F	F	F
USA	G	G	G	G	G	G	G	G	G	G	F	G	G	G
Venezuela	•	•	•	•	•	•	F	F	•	•	•	•	•	•
Viet Nam	--	F	--	F	F	F	--	--	--	•	F	F	F	F

G, patent(s) granted; F, patent(s) filed/pending; --, not filed/no patent application; •, data not available; *, patent rejected;

■ = Included in voluntary license agreements with Gilead (sofosbuvir+ledipasvir) and Bristol-Myers Squibb (daclatasvir). For sofosbuvir and ledipasvir of the EAPO countries, included are Kyrgyz Republic, Tajikistan and Turkmenistan and for declatasvir, included are Azerbaijan and Turkmenistan.

ARIPO, African Regional Intellectual Property Organization; GCC, Cooperation Council for the Arab States of the Gulf; EAPO, Eurasian Patent Organization; EPO, The European Patent Office; OAPI, Organisation Africaine de la Propriété Intellectuelle (African Intellectual Property Organization)

Notes: For each molecule, the first letter relates to the primary patent; the second letter combines information for all other secondary identified patents (except for sofosbuvir that has two primary patents)

For more comprehensive data on the patents and license agreements, please see the WHO Reports on the patent situation of key products for treatment of hepatitis C, updated June 2016: http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)*.

BOX 3.3. Voluntary license agreements for hepatitis C medicines

In 2014, the originator company of sofosbuvir granted non-exclusive licenses initially to seven Indian companies to produce generic versions of sofosbuvir and ledipasvir/sofosbuvir for use in 91 countries and later expanded to 11 Indian companies and 101 countries, and included the single-tablet regimen of sofosbuvir/velpatasvir. The agreements permit the licensees to manufacture and sell sofosbuvir, ledipasvir and velpatasvir in the licensing territory and thus enable 101 countries to procure generic products. This includes 31 low-income countries, two high-income countries (Equatorial Guinea and Seychelles), and 68 middle-income countries *(79)*.

The license agreement allows licensees to combine the licensed products with other DAAs owned by different producers, for example, daclatasvir, which enables the development of alternative generic combinations. The agreement also allows the licensees to sell products to countries that have issued a compulsory license for importation. The license agreement, in practice, does not allow the shipping of products to countries where any patent related to the respective DAA has been filed or granted. Licensees are obliged to procure their API only from licensed Indian API manufacturers, which limits the competition in the API market. The license requires the licensees to implement anti-diversion measures (*see* Box 4.1). It does not require the licensees to seek WHO prequalification *(77)*.

The originator company of daclatasvir signed a license agreement for daclatasvir with the Medicines Patent Pool in 2015, which had expanded its mandate to cover HCV and tuberculosis drugs in addition to those for HIV. By July 2016, the Medicines Patent Pool granted sublicenses to seven Indian generic manufacturers to produce daclatasvir for 112 LMICs, representing 69% of the burden of HCV in LMICs. This royalty-free license allows sub-licensees to combine daclatasvir with other medicines and to develop new generic FDCs. Contrary to the sofosbuvir license, the licensees are allowed to sell daclatasvir in countries not included in the licensing agreement if a patent has not been filed or granted, as long as they do not rely on the technology of the innovator company and use an alternative production process. This further expands the number of countries that can procure generic daclatasvir *(78)*.

Similar to the sofosbuvir agreement, licensees can sell products to countries that issue a compulsory license. The license requires the generic manufacturers to seek WHO prequalification or approval by a stringent regulatory authority. These license agreements include technology transfer and waive data exclusivity to facilitate the registration of generic products in the territory.

TABLE 3.2. List of countries included in voluntary licenses for sofobuvir and/or daclatasvir (as of June 2016)

	Voluntary license	
	daclatasvir	sofosbuvir
African Region		
Algeria		
Angola		
Benin		
Botswana		
Burkina Faso		
Burundi		
Cameroon		
Cabo Verde		
Central African Republic		
Chad		
Comoros		
Congo		
Côte d'Ivoire		
Democratic Republic of Congo		
Djibouti		
Equatorial Guinea		
Eritrea		
Ethiopia		
Gabon		
Gambia		
Ghana		
Guinea		
Guinea-Bissau		
Kenya		
Lesotho		
Liberia		
Libya		
Malawi		
Maldives		
Mali		
Madagascar		
Mauritania		
Mauritius		
Mozambique		
Namibia		
Niger		
Nigeria		
Rwanda		
Sao Tome and Principe		
Senegal		
Seychelles		
Sierra Leone		
Somalia		
South Africa		
South Sudan		
Sudan		
Swaziland		
Togo		
Tonga		
Uganda		
United Republic of Tanzania		
Zambia		
Zimbabwe		

	Voluntary license	
	daclatasvir	sofosbuvir
Eastern Mediterranean Region		
Afghanistan		
Egypt		
Iraq		
Morocco		
Occupied Palestine Territory		
Pakistan		
Syrian Arab Republic		
Tunisia		
Yemen		
European Region		
Azerbaijan		
Georgia		
Kyrgyzstan		
Turkmenistan		
Uzbekistan		
Region of the Americas		
Antigua and Barbuda		
Belize		
Bolivia		
Costa Rica		
Cuba		
Dominica		
Dominican Republic		
Ecuador		
El Salvador		
Grenada		
Guatemala		
Guyana		
Haiti		
Honduras		
Jamaica		
Nicaragua		
Panama		
Paraguay		
St Lucia		
St Vincent and the Grenadines		
Suriname		

	Voluntary license	
	daclatasvir	sofosbuvir
South-East Asia Region		
Bangladesh		
India		
Bhutan		
Democratic People's Republic of Korea		
Indonesia		
Myanmar		
Nepal		
Sri Lanka		
Timor-Leste		
Western Pacific Region		
Cambodia		
Cook Islands		
Lao People's Democratic Republic		
Fiji		
Kiribati		
Marshall Islands		
Micronesia		
Mongolia		
Nauru		
Niue		
Palau		
Papua New Guinea		
Philippines		
Samoa		
Solomon Islands		
Tuvalu		
Vanuatu		
Viet Nam		

	Included in licensing agreement
	Not included in licensing agreement

Sources: Gilead: access partnerships [website] (http://www.gilead.com/responsibility/developing-world-access/access%20partnerships, accessed 8 September 2016); and The Medicines Patent Pool signs first sub-licenses for hepatitis C medicine daclatasvir. In: Medicines Patent Pool [website]. Geneva: Medicines Patent Pool; 2015 (http://www.medicinespatentpool.org/the-medicines-patent-pool-signs-first-sub-licences-for-hepatitis-c-medicine-daclatasvir/, accessed 30 June 2016) *(77, 78)*.

3.5.3 Compulsory licensing

While countries included in the voluntary license agreements benefit from lower prices through generic competition, countries outside the territory where patents have been filed and granted may have to use other means to ensure affordable prices. Such measures can include price regulation, price negotiations, including under differential pricing schemes, as well as the use of the flexibilities of the TRIPS Agreement, which include compulsory licensing.

Contrary to a voluntary license, a compulsory license can be issued by a government to allow a local company to manufacture the patented product or to import it under certain conditions. The TRIPS Agreement contains certain conditions (Article 31) *(74)*. The procedure to grant a compulsory license is, however, governed by the respective national (patent) law, which has to define the specific grounds for which a compulsory license can be granted as well as the procedure to be followed.

Under a compulsory licence, countries can choose whether they want to import or locally produce the medicine. Unlike voluntary licenses, compulsory licenses are in principle limited mainly to the country that issued the license as they have to serve "predominantly for the supply of the domestic market" (Article 31 of the TRIPS Agreement). However, a mechanism put in place in 2003 allows World Trade Organization (WTO) Members to waive this condition to grant special compulsory licenses for the manufacture and export of generic medicines to countries that do not have local manufacturing capacities in order to supply the needed medicines to their patients (*see* http://www.who.int/phi/promoting_access_medical_innovation/en/ *(74)*). The system also includes provisions that can support the production or importation of medicines at the regional level. So far, no country has used compulsory licensing for any DAA.

It was reported in the media that Romania considered the use of this instrument to import generic DAAs *(80)*. Obtaining a market authorization for a generic import, however, would have been problematic. To legally import and distribute a medicine in Europe, the medicine needs to be authorized by the EMA for the European market to guarantee its quality, safety and efficacy, or by a national authority. European legislation prevents generic applicants, for at least eight years, from relying on the clinical trial data of the originator company to document the safety and efficacy of their product. This prevents the registration of generic sofosbuvir, for example, even in the absence of a patent or a compulsory license. Thus, unless the generic applicant reproduces its own data by conducting new clinical trials, which would be very costly and time-consuming (and raise ethical concerns), it will not be able to enter the market in the absence of a marketing authorization even if a compulsory license is granted, unless this compulsory license also waives the data exclusivity. Furthermore, experiences from middle-income countries that have used standard compulsory licenses show that they are likely to face political pressure by other countries as well as the pharmaceutical industry and its lobby groups.

As outlined in the *Global strategy and plan of action on public health, innovation and intellectual property*, WHO provides, upon request, in collaboration with other competent organizations, technical support to countries that intend to make use of the flexibilities contained in the TRIPS Agreement as recognized by the Doha Declaration on the TRIPS agreement and public health *(81)*. Further information can be found in the WHO *Guide for the application and granting of compulsory licences and authorization of government use of pharmaceutical patents (82).*

3.6. Procurement

Sound procurement mechanisms are a prerequisite to ensure the availability and affordability of essential medicines in general. While it is beyond the scope of this report to describe the characteristics and principles of a good pharmaceutical procurement scheme, pooling procurement is one option that is highlighted. Pooled procurement, whereby several countries negotiate prices as one entity, can be more efficient and allows countries to get volume-based discounts. Regional negotiations can improve procurement, as the example of Organisation of Eastern Caribbean States (OECS)/Pharmaceutical Procurement Service or the Gulf Cooperation Council (GCC) Procurement System has shown. Brazil, along with a number of other Latin American countries, has jointly negotiated a price of US$ 2292 for a 28-day supply, for the procurement of sofosbuvir from the originator company *(83)*.

Well-planned procurement and efficient pharmaceutical production is aided by reliable information on the projected treatment needs. For HIV, demand forecasting is an essential tool to ensure regular supply. This demand forecasting is challenging for hepatitis because of the uncertainty in the numbers of people with HCV infection and varying treatment eligibility criteria in different countries. The lack of international funding or procurement mechanisms also leads to a more scattered market than for HIV, which further complicates reliable demand forecasting.

4. OVERCOMING ACCESS BARRIERS: EXAMPLES FROM SELECTED COUNTRIES[2]

4.1. Approaches in different countries

The following section presents examples of certain countries that have made HCV treatment more widely available for their populations. The different country responses highlight how countries that were able to obtain affordable prices for DAAs were able to commit to treatment scale up and implement national treatment programmes (e.g. Egypt). Some countries have negotiated with originator companies, but even so, prices remain high, leading to treatment prioritization or rationing (e.g. Argentina, Brazil, Romania). Civil society groups in some middle-income countries have filed patent oppositions (e.g. Argentina, Brazil, Thailand and Ukraine). In some countries where the patent situation allows for it, local production of generics has resulted in lower prices (e.g. Argentina, Egypt, Morocco and Pakistan). Some countries are relying on donations or programmes run by NGOs to start providing treatment (e.g. Georgia, Ukraine). Rwanda is an example of a low-income country that is developing a national treatment programme. Table 4.1 presents a summary of findings of the WHO survey conducted in 13 countries on improving access to DAA medicines.

[2] Unless otherwise noted, the information in this chapter comes from the WHO survey on access to DAAs in selected countries.

BOX 4.1. Egypt's response to hepatitis C

The prevalence of HCV in Egypt is among the highest in the world (7% among 18–59 years age group) *(84)*. Initially, the virus was spread through reuse of syringes in a national anti-schistosomiasis campaign. Now, unsafe medical injections, inadequate infection control and intrafamilial transmission are driving transmission, which was estimated at 150 000 new cases each year *(8, 84–88)*. Thus, improving infection control remains a major challenge and a prerequisite for controlling the spread of the virus. Egypt has treated more people than any other low- or middle-income country. In 2015, approximately 170 000 people were treated with DAAs in the public sector. In 2016, 500 000 more people started DAA-based treatment between January and September 2016.

The groundwork for Egypt's response to HCV was undertaken a decade ago, when Egypt's Ministry of Health (MoH) established a National Committee for Control of Viral Hepatitis. In 2012, the MoH and the National Committee worked with partners to create Egypt's Plan of Action for the Prevention, Care and Treatment of Viral Hepatitis, 2014–2018, which was updated to include DAAs in 2014. Over 90% of Egyptians with hepatitis C are infected with genotype 4, which simplifies treatment selection and procurement *(89)*. Egypt's Plan of Action addresses pricing and affordability, procurement processes, surveillance, infection control, blood safety, prevention via vaccination for hepatitis B, care and treatment, provider and community education, and a research agenda *(90)*.

Egypt entered into price negotiations for DAAs soon after these medicines were introduced to the market and became the first country to negotiate a large reduction in the price of sofosbuvir with the originator company. At US$ 300 for a 28-day supply, it was at the time the lowest price in any country *(91)*. As one patent on sofosbuvir was rejected in the examination process and other relevant patents on sofosbuvir were not filed or granted, the treatment programme has been able to diversify procurement to include local companies, which has lowered the price for a 28-day supply to US$ 51.

Daclatasvir is available from the originator company at US$ 167 for a 28-day supply. Local production of daclatasvir by generic producers has reduced prices down to US$ 7 for a 28-day supply in the public sector, the lowest price in the world. Assuring the quality of locally produced DAAs remains key to ensuring the success of the treatment programme and preventing the development of drug resistance (*see* section 3.3).

Several factors have made Egypt's HCV Programme a success:

- high level of commitment from the president and government;
- high level of awareness among the population;
- an established National Committee to develop and implement plans and programmes;
- a national network of treatment centres;
- effective price negotiations with originator companies for pegylated interferon and DAAs soon after they came on the market;
- local production of affordable generic and biosimilar HCV medicines;
- predominance of a single genotype, which facilitates the selection of treatment regimens;
- a patient online treatment registration system.

During the past two years since introduction of the DAAs to the hepatitis treatment protocol in Egypt, the Egyptian Government spent around 2.8 billion L.E. (US$ 350 million) for the HCV national treatment programme. Almost 88% of treated patients were sponsored by the government whereas 12% of patients paid out of pocket. Egyptians pay up to six times more for their HCV treatment in the private market *(90)*.

4.2. Generic competition and local production

Generic competition is the most effective way to drive down prices for medicines. In the case of HIV treatment, generic competition, streamlined procurement mechanisms and economies of scale have reduced the price of a first-line antiretroviral regimen by 99%, from US$ 10 000 per person per year to US$ 100 per person per year *(92)*.

Argentina is a high-income country, and therefore not included in voluntary licensing agreements. Sofosbuvir is registered by the originator company in Argentina but is not under patent as the applications are under review. This has allowed a local company to produce generic sofosbuvir *(93)*. In Argentina, the price per patient-month for sofosbuvir from the local generic producer is US$ 501 (versus US$ 2086 for sofosbuvir from the originator company). However, costs of the generic product are still high as compared with other countries and suppliers. Whether local production can continue in the long run depends on the outcome of the patent examination procedure.

Although Argentina is currently limiting treatment to a total of 1200 people with cirrhosis, a second phase is planned, which will provide treatment to persons without cirrhosis, people with HIV/HCV coinfection and those with serious extrahepatic manifestations. A strong civil society movement is pushing for increased access to DAAs. Fundación Grupo Efecto Positivo, the Argentinian Network of Positive People (Redar Positiva) and Initiative for Medicines, Access & Knowledge (I-MAK) have filed a patent opposition against sofosbuvir.

Morocco established its national HCV programme in 2012; it provides HCV diagnostics, genotyping and liver disease staging, and has treated over 1700 people with pegylated interferon and ribavirin. The country is currently developing a national strategy and updating its treatment guidelines. The primary patents for sofosbuvir, ledipasvir and daclatasvir were not filed in Morocco, allowing for local production and importation of generic products. While Morocco was not included in the initial license agreement on sofosbuvir, ledipasvir and velpatasvir, it was added when the geographical scope was expanded. Morocco is also included in the voluntary licensing agreement for daclatasvir and can thus procure the API for these DAAs from licensed suppliers as well. The Minister of Health of Morocco has announced the goal of "Morocco without hepatitis C in 2030" *(33)*. Morocco also benefits from a strong civil society movement, including the International Treatment Preparedness Coalition-Middle East North Africa (ITPC-MENA) and The Association against AIDS (ALCS), the "Collectif pour le droit à la santé Maroc" that lobby for increased access.

Pakistan has one of the world's highest HCV prevalence rates. Over 257 000 people have been treated with interferon and ribavirin. The MoH is updating the country's HCV treatment guidelines to include DAAs and planning to distribute sofosbuvir via public sector programmes. In Pakistan, the primary patents on sofosbuvir have not been filed. Some secondary patents are pending. Local companies have used this situation to enter the market with generic products. Pakistan is included in the voluntary licencing territories for sofosbuvir and daclatasvir, and can thus also procure generic products from the respective licensees. Sofosbuvir has been registered, and registration of daclatasvir is pending. Sofosbuvir is already available through the private sector, sold by local and foreign companies that signed the license agreements. In the private sector, 47 035 people were treated with a sofosbuvir-based regimen from August 2014 through January 2016, and nearly 37 000 people have started treatment since February 2016. Generic competition has resulted in prices of US$ 15 for a 28-day supply of sofosbuvir from a local generic producer, the lowest price in the world (*see* section 3.1 and Chapter 5. Drug profiles).

4.3. Civil society advocacy fuels negotiations

In **Thailand**, civil society groups have been lobbying for access to hepatitis C medicines for nearly a decade. Thai civil society has protested against the high DAA prices and filed a patent opposition against one patent application for sofosbuvir *(94)*. Thailand is not included in the voluntary licensing agreements. The primary patent for daclatasvir is under examination. Thailand has a national programme for HCV, under the National Health Security Office (NHSO). The NHSO is the public body in charge of implementing universal health coverage established by Thai Law. Treatment supported by the NHSO consists of pegylated interferon and ribavirin. The NHSO also offers financial support of up to US$ 300 per patient for the costs of laboratory tests. The Thai government is engaging in price negotiations with originator companies to introduce DAAs in the public sector.

4.4. Political will

Strong political will and civil society engagement in **Brazil** led the country to provide free HIV treatment. In 2002, the country established a national hepatitis programme. In 2011, the MoH distributed rapid HCV test kits to its counselling and testing centres, expanded its laboratory network, and set up a referral system for people who were diagnosed with hepatitis C. Brazil is not included in the voluntary licensing agreements. Brazil concluded pricing negotiations with originator companies and later engaged in joined negotiations with the Mercosur countries and their Associated States *(83)*.

Brazil updated the national treatment guidelines in 2015 to include DAAs. Brazil provides HCV treatment at no charge for eligible patients. Now, sofosbuvir, daclatasvir and simeprevir are available at national, provincial and district hospitals, at district clinics and some pharmacies, although access is currently limited to people with moderate-to-serious liver damage (METAVIR score ≥F2).

4.5. Efficient regulatory processes for rapid scale up

Rwanda is the only low-income country to have registered sofosbuvir, daclatasvir and sofosbuvir/ledipasvir at the time the survey was conducted. Although the country faces many challenges (lack of awareness, limited access to diagnostics and treatment, need for provider education), rapid progress has been made. A national hepatitis programme was established in 2011. Rwanda began working on HCV in 2015 and has already issued DAA-inclusive treatment guidelines. Rapid HCV tests are being validated, training for doctors and nurses at provincial and referral hospitals is under way, and will be expanded to include pharmacists, laboratory technicians, nutritionists and counsellors to facilitate decentralization of care.

Rwanda is included in the voluntary licensing agreements and can procure a 28-day supply of sofosbuvir/ledipasvir from the originator company at US$ 400 under the differential pricing policy of the company. Rwanda's public and private insurers cover 85–90% of treatment costs for 20% of the population. The remaining 80% of the population depends on community-based health insurance, which is considering provision of HCV treatment.

4.6. Starting out

In January 2016, the **Philippines** MoH convened a Technical Working Group on Viral Hepatitis. At the same time, the MoH met with doctors and patients about HCV treatment needs, and held pricing negotiations with companies.

The country is included in the licensing agreements for sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir and daclatasvir, and thus can procure generic products from the licensees. While patents for sofosbuvir have been filed and one granted, the patent situation for daclatasvir is likely to allow for import or local production independent of the license agreement (*see* Table 3.1, Table 3.2 and http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)*). Registration for these DAAs is either planned or under way. Sofosbuvir was registered by the originator company in mid-2015, and registration for sofosbuvir/ledipasvir was filed in 2015. Once these DAAs become available, the country will need political will, a national plan, treatment guidelines, a budget for providing treatment to people living with HCV infection and training for health-care providers.

4.7. Building on a national plan and adopting treatment guidelines

Treatment guidelines provide a framework for standardized treatment and quality care, and facilitate reimbursement. Although DAAs have made HCV treatment much simpler, health-care providers will still need guidance on how to diagnose, stage and cure people with HCV.

Georgia's small size and population, high HCV prevalence (~6%) and strong civil society advocacy led the country to take a bold step: develop a national hepatitis C elimination plan. To assist in the planning and implementation, the government sought technical assistance from WHO, the US Centers for Disease Control and Prevention (CDC), and international clinical experts. Technical assistance was provided to the MoH to conduct a national population-based HCV survey, which gave a better picture of the prevalence and distribution of HCV infections in the country *(32)*.

Since 2011, Georgia had been providing pegylated interferon and ribavirin to people with HIV/HCV coinfection, with support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). The treatment programme was expanded to cover prisoners and then the general population. Once DAAs came on the market, Georgia began discussions with an innovator company about becoming a test case for HCV elimination. It prepared a comprehensive national programme, including prevention, surveillance and data management systems, assessment of laboratory capacity and drug procurement, and training. Georgia's HCV elimination programme was launched in 2015. Initially, it focused on subsidizing HCV diagnostics and treating 5000 people with severe liver disease, using pegylated interferon, ribavirin and sofosbuvir under a donation programme with the originator company *(32)*.

Georgia plans to expand treatment coverage to 20 000 people per year, using a sofosbuvir-based regimen under the donation programme. The Georgia programme includes strict anti-diversion measures that may compromise adherence and treatment outcomes. These include requiring proof of identity and citizenship, photographing people taking their first dose of medication and dispensing only a month's supply of medicine at a time, contingent on the return of empty pill bottles or viral load testing. It is important that anti-diversion measures do not impede access or lead to discrimination (*see* Box 4.2).

BOX 4.2. Anti-diversion measures

The existing large price discrepancies and lack of access to affordable medicines increase the possibility of product diversion from countries where treatment is less expensive to countries where it is more expensive. Pharmaceutical companies, national treatment programmes and private distributors thus implement what are called anti-diversion measures. Possible specific measures include product packaging that is specific to the treatment programme, different trade names, different colour of tablets and electronic tracking tools. Concerns have been raised about anti-diversion measures that have been implemented in relation to the new HCV medicines. Current reported practices to control the individual diversion of medicines include the following:

- distribution of medicines with bar codes that include some patient information;
- access to medicines provided on a named patient basis with proof of identification;
- requiring proof of residence and citizenship before providing access to medication;
- photographing the patient when he/she picks up the first bottle of medicine;
- distribution of a limited (e.g. 2 weeks or 1 month) supply of medicine at a time, with the requirement that empty medicine bottles be brought or sent back in exchange for new bottle(s);
- requiring documentation of a negative viral load result if a patient fails to return an empty bottle of medicine (to prove that the patient has been taking the medicine rather than having sold it).

Preventing diversion of medicines is a legitimate concern. However, it is important that anti-diversion measures operate within the bounds of medical ethics. These include the following:

- Confidentiality of patient information – access to patient-identifying information should be restricted to health-care providers caring for the patient.
- Autonomy – patients have a right to make decisions about their health care, including stopping treatment if they so choose.
- Privileged physician–patient interaction – treatment decisions should be made by health-care workers providing care to a patient.
- Proportionality – anti-diversion measures should not put an undue burden on patients, health-care workers and treatment programmes.
- Non-discrimination – anti-diversion measures should not directly or indirectly restrict access to care for vulnerable and marginalized communities such as refugees, PWID, migrants, homeless persons or those with unstable living arrangements.

Source: Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1, accessed 13 April 2016).

Indonesia's national HCV plan grew from an existing viral hepatitis plan established in 2011. In 2013, the Minister of Health announced that the country would provide HCV treatment in 2014, but DAAs were not yet on the market. Nonetheless, the national treatment guidelines include preferred and alternative DAA regimens (sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, sofosbuvir/simeprevir and sofosbuvir/ribavirin).

Application for market authorization is pending and generic versions of sofosbuvir, daclatasvir and sofosbuvir/ledipasvir should become available, as Indonesia is included in the licensing territories for these DAAs. In addition, the primary patent for daclatasvir and most of the relevant secondary patents have not been filed in Indonesia (*see* Table 3.1).

Some challenges remain: awareness of HCV and access to diagnostics are limited, especially for PWID. Currently, the price for hepatitis C testing and pre-treatment assessment can be as high as US$ 580, triple the average monthly salary.

Nigeria has a national hepatitis plan in place since 2013. To prepare for treatment roll-out, the country began drafting guidelines before DAAs were registered. The guidelines will include sofosbuvir and sofosbuvir/ledipasvir, daclatasvir, and paritaprevir/r/ombitasvir plus dasabuvir. The MoH is planning to release the guidelines as soon as DAAs become available – but the requirement for local clinical trials may slow down registration and access. The WHO Patent landscape reports *(26)* identified no patents on sofosbuvir, ledipasvir, daclatasvir in Nigeria, which is also included in the respective license agreements, opening all possibilities for the procurement of generic DAAs (*see* Table 3.1).

Romania updated its hepatitis C treatment guidelines in 2015 to include DAAs; interferon has been recommended since 2008. Currently, high prices have prevented widespread access to DAAs through the public sector. Romania is not included in the license agreements. Its situation in the heart of Europe with the possibility of parallel exports to other European countries will make significant price reductions challenging. Access to interferon-free treatment is limited to people with cirrhosis or people with pre-cirrhosis who cannot tolerate interferon, and in liver transplant recipients with recurrent HCV. Since November 2015, sofosbuvir, sofosbuvir/ledipasvir, daclatasvir, simeprevir, and paritaprevir/r/ombitasvir plus dasabuvir have been available at district hospitals. A 28-day supply of sofosbuvir is procured at US$ 16 368 from the originator and a 28-day supply of daclatasvir is procured at US$ 10 289 from the originator company (*see* Table 4.1. for prices of the other DAAs in Romania, and section 3.5.3).

4.8. Donor support and NGO partnerships

Ukraine is a middle-income country that is not included in the licensing agreements. To help ensure access to affordable treatment, the Alliance for Public Health, an NGO, negotiated a price reduction with the originator company for sofosbuvir and is providing sofosbuvir-based treatment at US$ 300 for a 28-day supply. The Alliance began treating persons with HIV/HCV coinfection and has since expanded to provide HCV treatment to PWID. In less than six months, the Alliance had treated 271 people; the cure rate among the 125 people who completed therapy was 89%. With support from the MoH, the project is expanding to 17 sites and plans to treat 750 people by the end of October 2016.

In 2015, despite massive challenges in high prices and drug availability, the survey showed that countries are taking up the challenge to increase access to new treatments for hepatitis C. Factors for success included country leadership, adopting national protocols with new DAA treatment, price negotiation, and greater generic availability. Some of the countries such as Brazil, Egypt and Pakistan have emerged as pioneers in overcoming barriers and achieving accelerated access to what is now considered a public health priority. WHO will continue to play a strong role in policy guidance and responsive support to countries for enabling access to new hepatitis C drugs.

TABLE 4.1. Overcoming access barriers: summary from selected country examples

Country, income category	National plan and treatment guidelines	Registered DAAs (company)	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Voluntary licensing (VL)	Compulsory licensing	Generic local production[1]	Government commitment/ strategy	Civil society activities
Argentina High-income	Yes, currently phasing in DAA-based treatment; initially targeting 1200 patients with stage F4 fibrosis	daclatasvir (BMS)	$1286	$9692	No	No	Yes	Use locally produced generic and negotiate lower price for branded sofosbuvir; gradual treatment scale up	Patent opposition for sofosbuvir, protests demanding treatment access
		sofosbuvir (Gilead)	$2086	$5737					
		sofosbuvir (Richmond)	$501	$4278					
		ombitasvir/ paritaprevir/ritonavir and dasabuvir (AbbVie)							
Brazil Upper–middle-income	Yes, currently restricted to ≥F2 fibrosis; 7462 treated with DAAs in 2015	daclatasvir (BMS)	$850		No	No	No	Regional price negotiations with originator companies	Patent opposition, protests demanding treatment access
		simeprevir (Janssen)	$866						
		sofosbuvir (Gilead)	$2292						
Egypt Lower–middle-income	Yes, 170 000 people treated with DAA-based treatment in 2015, and 500 000 people more between January and September 2016	daclatasvir (BMS)	$167		sofosbuvir, sofosbuvir/ ledipasvir, sofosbuvir/ velpatasvir	No	Yes	Use locally produced generics (VL and non-VL) and price negotiations	Patent opposition; pressure to expand treatment to all
		daclatasvir (EVA Pharma, AUG pharma, AstraZeneca Pharmaceuticals, Marcyrl, Mash Pharma, European Egyptian Pharmaceutical Industries, Future Pharmaceutical Industries)	$7						
		simeprevir (Janssen)	$250						
		sofosbuvir (VL Pharmed and Magic Pharma)	$300						
		sofosbuvir (Pharco and 14 other companies)	$51	$76					
Georgia Lower–middle-income	Yes, with an elimination plan developed and approved in 2015; 5000 people treated in 2015, and 14 300 people more between January and September 2016	sofosbuvir	Donation programme		daclatasvir	No	No, but possible	Scaled up elimination programme is under way, technical partnership with Centers for Disease Control and Prevention (CDC)	Advocacy to provide treatment for people who inject drugs and participation in development of elimination plan

Country, income category	National plan and treatment guidelines	Registered DAAs (company)	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Voluntary licensing (VL)	Compulsory licensing	Generic local production[1]	Government commitment/ strategy	Civil society activities
Indonesia Lower–middle-income	Yes, HCV programme established in 2014; guidelines recommend DAAs	sofosbuvir (Indian generic producers)	$280		sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, daclatasvir	No	No	Registration of originator simeprevir is under way	Pressure to broaden access for people who inject drugs, work to reform patent law
Morocco Lower–middle-income	National programme in 2012, currently developing national plan and updating treatment guidelines to include DAAs	daclatasvir (Pharma 5)	$120	$150	daclatasvir, sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir	No	Yes	Target "Morocco without hepatitis in 2030"	Pressured to include the country in the voluntary licensing territories, and to broaden access for people who inject drugs
		sofosbuvir (Pharma 5)		$300					
Nigeria Lower–middle-income	Treatment guidelines being drafted; release planned in 2016				daclatasvir, sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir	No	No, but possible	Registration of originator and generic DAAs are under way	
Pakistan Lower–middle-income	Yes, 47 035 people treated with sofosbuvir-based regimen via private sector programme in 2015 MoH is updating the country's HCV treatment guidelines to include DAAs	sofosbuvir	$300	$300	daclatasvir, sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir	No	Yes	Plan for delivering DAAs via public sector programmes is under way	
		sofosbuvir/ledipasvir		$420					
		sofosbuvir (VL generic)	$56						
		sofosbuvir (non-VL, including Getz Pharma)	$15–42						
Philippines Lower–middle-income	MoH convened "Technical Working Group on Viral Hepatitis" in 2016 to consult with doctors and patients				daclatasvir, sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir	No	No, but likely to be possible for daclatasvir	Registration of originator and generic DAAs are under way	
Romania Upper–middle-income	Treatment guidelines updated in 2015 to include DAAs, restricted to F4 fibrosis genotypes 1 and 4 infection, F4 fibrosis with HIV infection, patient with post liver transplant and F3 fibrosis with intolerance to interferon	daclatasvir	$10 289		No	No	No	Negotiation with originators	Pressure to issue a compulsory license for sofosbuvir
		ombitasbvir/paritaprevir/ritonavir and dasabuvir	$16 145	$17 632					
		ombitasbvir/paritaprevir/ritonavir	$14 753						
		simeprevir	$9431						
		sofosbuvir	$16 368						

Country, income category	National plan and treatment guidelines	Registered DAAs (company)	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Voluntary licensing (VL)	Compulsory licensing	Generic local production[1]	Government commitment/ strategy	Civil society activities
Rwanda Low-income	Yes, treatment guidelines updated in 2015 to include DAAs	sofosbuvir + daclatasvir	$300 for the two DAAs		daclatasvir, sofosbuvir, sofosbuvir/ ledipasvir, sofosbuvir/ velpatasvir	No	No, but possible	Negotiation with originators, registration of generic DAAs under way, training and decentralization; community-based health insurance	
		sofosbuvir/ ledipasvir	$400						
Thailand Upper–middle-income	National programme currently offers pegylated interferon/ ribavirin; coverage of DAAs likely if pricing negotiations with originators are successful	sofosbuvir (Gilead) and daclatasvir (BMS)		$3700 for the two DAAs	No	No	No	Possibility of local production; negotiations with originators are under way	Pressure to provide treatment, and to broaden access to include people who inject drugs; protesting high DAA prices; patent opposition
Ukraine Lower–middle-income	MoH has updated treatment guidelines to include DAAs for some populations; limited resources to support diagnostics or treatment; 271 HCV/ HIV-coinfected people treated by Alliance for Public Health in 2015 under grant from Global Fund to Fight AIDS, Tuberculosis and Malaria	sofosbuvir	$300		No	No	Likely to be possible for some DAAs, see the patent situation in Table 3.1. Data exclusivity may prevent registration and procurement	Support expanding programme to 17 sites with plans to treat 750 people during 2016; registration of generic sofosbuvir under way	Massive protests to demand treatment, especially for people who inject drugs; NGO-led screening, and negotiations for DAAs; NGO-run treatment programme for people with HIV/HCV and people who inject drugs

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[1] For the patent situation, *see* Table 3.1 and http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)*.

5. DRUG PROFILES[3]

These profiles include information on the registration status, pricing and production of DAA medicines collected by WHO through a survey of originator and generics companies. The patent information stems from the WHO reports on the patent situation of key products for treatment of hepatitis C, as updated in June 2016 *(26)*. The objective is to increase transparency, share information with all partners and countries and, ultimately, to facilitate HCV treatment scale up. This chapter provides information on DAAs that are recommended in the 2016 WHO hepatitis C treatment guidelines: daclatasvir, ombitasvir/paritaprevir/r plus dasabuvir, simeprevir, sofosbuvir and sofosbuvir/ledipasvir *(20)*.

[3] Unless otherwise noted, the information in this chapter comes from the WHO survey of DAA pricing, licensing, registration and production, and the WHO reports on the patent situation of key products for treatment of hepatitis as updated in June 2016 *(26)*.

5.1. Daclatasvir

General information

Therapeutic class: NS5A inhibitor

Originator company: Bristol-Myers Squibb

First approval was on 27 August 2014, by the EMA. Initially approved for use with other medicines in infection with HCV genotypes 1, 2, 3 and 4, the EMA on 28 January 2016 expanded the indication to include the use of daclatasvir/sofosbuvir ± ribavirin in people with decompensated cirrhosis, HIV/HCV coinfection and in post-transplant patients.

The US FDA approved daclatasvir for use with sofosbuvir in people infected with HCV genotype 3 on 24 July 2015. On 5 February 2016, the indication was expanded to include HCV genotype 1, and daclatasvir/sofosbuvir ± ribavirin approved for use in people with decompensated cirrhosis, HIV/HCV coinfection and post-transplant patients.

2016 WHO Guidelines

Preferred regimen: daclatasvir used with sofosbuvir ± ribavirin for 12 or 24 weeks, in people with or without cirrhosis who are infected with HCV genotypes 1, 3 and 4.

Alternative regimen: daclatasvir with sofosbuvir for 12 weeks, for people with or without cirrhosis who have HCV genotype 2 infection.

Dosing: 30, 60 or 90 mg, once daily.

WHO Model List of Essential Medicines. In April 2015, daclatasvir was included in the nineteenth edition of the WHO EML and in the thirteenth invitation to submit an expression of interest (EOI) for product evaluation in the WHO Prequalification Programme.

Patents. There are a number of patents covering the base compound of daclatasvir, crystalline forms, combinations with other DAAs and manufacturing processes. The most important patent is the one covering the compound WO2008021927. It has been filed widely in high-income countries, but in relatively few LMICs. Of the countries included in the WHO reports on the patent situation, it has not been filed in ARIPO, Costa Rica, Ecuador, Ethiopia, Georgia, Indonesia, the Islamic Republic of Iran, Jordan, Malaysia, Morocco, Nigeria, OAPI, Pakistan, the Philippines, Ukraine, Uruguay and Viet Nam. It has been rejected in Egypt *(26)*. Secondary patents can be relevant in certain cases, for example for particular combinations, but most of these countries should be able to locally produce daclatasvir or procure generic daclatasvir. Most of these countries are also included in the territory of the license agreement, which enables these countries to procure generic products from licensed manufacturers as well. For further details on the patent situation, *see* http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)* and Tables 3.1 and 3.2.

Registration. Bristol-Myers Squibb, the originator company, registered daclatasvir in Argentina, Brazil, Bulgaria, Colombia, Egypt, Lebanon, Mexico, Peru, the Philippines, Rwanda, Romania, Thailand and Ukraine. Among generic manufacturers, Hetero and Natco have obtained marketing authorization in India, Incepta in Bangladesh, and Pharma 5 in Morocco.

Currently, no generic daclatasvir products have been prequalified by WHO.

WHO Prequalification. Daclatasvir 30 mg and 60 mg from the innovator company was WHO pre-qualified in October 2016. Currently, no generic daclatasvir products have been prequalified by WHO.

Pricing and access. Prices for a 28-day supply of daclatasvir range from US$ 21 000, the originator price in the USA, to US$ 61 for generic versions in India and US$ 7 in Egypt *(64)*.

Daclatasvir is relatively cheap to produce. According to recent estimates that include a 50% profit margin, packaging and formulation costs, a 28-day supply of daclatasvir could be sold for approximatively US$ 5.5.[4]

In November 2015, Bristol-Myers Squibb entered into a royalty-free voluntary licensing agreement for daclatasvir with the Medicines Patent Pool (*see* for further details Box 5.1). The daclatasvir voluntary licensing agreement enables generic manufacture of daclatasvir for sale in 112 LMICs (*see* Table 3.2). Licensees have to obtain approval from the WHO Prequalification Programme, or a stringent drug regulatory authority. Data protection is waived, and licensees are authorized to sell outside the licensed territory, so as long as they do not use the technology transferred from the originator company, and do not infringe patents. The voluntary licensing agreement allows the licensees to develop FDCs with other DAAs not owned by Bristol-Myers Squibb.

So far, seven companies have signed the licensing agreement with the Medicines Patent Pool (Aurobindo, Cipla, Emcure, Hetero, Laurus, Natco and Zydus Cadila). Two of them, Hetero and Natco, are reported to be manufacturing daclatasvir and marketing it at least in India. Several other companies have started marketing finished formulations of daclatasvir (having purchased the API from Natco) in the local Indian market (Sun Pharmaceuticals Ltd, Mylan Pharmaceuticals Pvt. Ltd, Cadila Healthcare Ltd and Abbott India Ltd). Cipla sells the finished formulation of daclatasvir (API obtained from Hetero) in the local Indian market.

Several companies are making daclatasvir available outside of the licensing agreement in countries where there are no patents as in Bangladesh, Egypt and Morocco.

Known API sources include Xiamen Halo Biotechnology Ltd. (supplying Incepta), Laurus (supplying Natco) and Hetero Labs.

While the Medicines Patent Pool license includes more than two thirds of all middle-income countries, it does not include several middle-income countries with a high HCV prevalence, including Brazil (1.9 million), China (8.9 million), Mexico (0.9 million), Thailand (0.9 million) and Ukraine (0.9 million).

TABLE 5.1. Prices of generic daclatasvir 60 mg, per 28-day supply, reported from Bangladesh, Egypt, India and Morocco

Manufacturers	Marketing companies/distributors	Country	Local market		Export	
			Public	Private	Public	Private
Incepta Pharmaceuticals Ltd.	Incepta Pharmaceuticals Ltd.	Bangladesh	N/A	$141		
	Beximco Pharmaceuticals Ltd.		N/A	N/A		
EVA Pharma, AUG pharma, AstraZeneca Pharmaceuticals, Marcyrl, Mash Pharma, European Egyptian Pharmaceutical Industries, Future Pharmaceutical Industries	EVA Pharma, AUG pharma, AstraZeneca Pharmaceuticals, Marcyrl, Mash Pharma, European Egyptian Pharmaceutical Industries, Future Pharmaceutical Industries	Egypt	$7	N/A	N/A	N/A
Natco Pharma Ltd.	Natco Pharma Ltd	India	$61–70	N/A	$70	N/A
	Abbott India Ltd		$61	N/A	N/A	N/A
	Mylan Ltd		$61			
	Sun Pharmaceuticals Ltd			N/A	N/A	N/A
	Zydus Heptiza (division of Cadila Healthcare Ltd)		$61–100	N/A	N/A	N/A
Hetero Labs	Hetero Labs	India	$61–80	$100	$80	$100
	Cipla Ltd		N/A	N/A	N/A	N/A
Pharma 5	Pharma 5	Morocco	$120	$150	N/A	N/A

Note: All prices in US dollars. Hetero and Natco prices based on the exchange rate of US$ 1=65 Indian Rupees. N/A: not available

[4] Hill A, Simmons B, Gotham D, Fortunak J. Significant reductions in cost of generic production of sofosbuvir and daclatasvir for hepatitis C treatment in low- and middle-income countries. European Association for the Study of the Liver, International Liver Congress 2016, Barcelona, Spain, 13–17 April 2016.

5.2. Ombitasvir/paritaprevir/ritonavir ± dasabuvir

General information

Therapeutic class: FDC of a boosted HCV protease inhibitor and an NS5A inhibitor plus a non-nucleoside polymerase inhibitor

Originator company: Abbvie

First approval was on 19 December 2014 by the US FDA for use in infection with genotype 1 and on 24 July 2015 for use in infection with genotype 4.

2016 WHO Guidelines

Alternative regimen: for genotype 1 infection; for subtype 1a, use with ribavirin for 12 weeks (no cirrhosis) or 24 weeks (compensated cirrhosis). For subtype 1b, use for 12 weeks without ribavirin (no cirrhosis) or with ribavirin (compensated cirrhosis).

Alternative regimen: for genotype 4 infection (without dasabuvir); use with ribavirin for 12 weeks (no cirrhosis) or 24 weeks (compensated cirrhosis).

The combination is considered an alternative regimen because of safety issues (in people with decompensated cirrhosis, it can cause liver failure and death); drug–drug interactions with HIV treatment, certain hormonal contraceptives and other medicines; because it is effective against infection only with genotypes 1 and 4, and because it is a twice-daily regimen.

Dosing: FDC of ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg once daily ± dasabuvir 250 mg twice daily ± ribavirin twice daily

WHO Model List of Essential Medicines. In April 2015, ombitasvir/paritaprevir/ritonavir and dasabuvir were included in the nineteenth edition of the WHO EML, and in the thirteenth invitation to submit an EOI for product evaluation in the WHO Prequalification Programme.

Patents. For all three DAAs of the combination, a number of patents are pending or granted. There are primary patents claiming the compounds of paritaprevir, ombitasvir and dasabuvir as well as patents that claim combinations of these DAAs, other combinations as well as additional secondary patents. The WHO patent report on ombitasvir/paritaprevir/dasabuvir lists 20 different patent families covering the combination. The fact that the treatment combines three different molecules with different patents filed for each molecule makes it more challenging for generic companies to circumvent patents where granted. For further details, *see* http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)* and Table 3.1.

Registration. The originator company reported registration information. In LMICs, the dual combination was approved in Egypt. For the triple combination (ombitasvir/paritaprevir/ritonavir plus dasabuvir), it was approved in Albania, Azerbaijan, Bosnia and Herzegovina, Brazil, Colombia, Costa Rica, Egypt, Malaysia, Mexico, Serbia and Tunisia, and filed in Belarus, Dominican Republic, Ecuador, Jamaica, Panama and Thailand. Submissions are under way in Moldova, Morocco and South Africa.

Pricing and access. In the United States, ombitasvir/paritaprevir/ritonavir and dasabuvir was launched at US$ 83 390/treatment course (although the company has offered significant discounts to US private payers in return for exclusivity of sales).

The originator company of ombitasvir/paritaprevir/ritonavir plus dasabuvir has not developed a comprehensive medicines access programme or entered into a license agreement. It uses a case-by-case “access pricing” approach for Africa and other low- and lower–middle-income

countries. Price negotiations are under way in Algeria, Moldova, Morocco, South Africa, Tunisia and Ukraine. The price in Romania is US$ 16 145 for a 28-day supply of ombitasvir/paritaprevir/ritonavir plus dasabuvir.

The company grants compassionate use and/or early access on a case-by-case basis, based on therapeutic need and eligibility. Through its early access programme, the company is currently providing treatment on a named patient basis in Mongolia, Tunisia, Ukraine and Viet Nam.

In the absence of license agreements and because of patent protection around all three components of the treatment, and due to the complexity of the combination, there are no generic versions approved in any country so far. None of the generic manufacturers surveyed indicated that it intends to develop a generic version.

5.3. Simeprevir

General information

Therapeutic class: HCV protease inhibitor

Originator company: Janssen

First approval on 22 November 2013 (US FDA)

2016 WHO Guidelines

Alternative regimen: simeprevir is part of an alternative regimen, recommended for use with sofosbuvir in genotypes 1 and 4 infection for people without cirrhosis; in people with cirrhosis with genotypes 1 and 4 infection, either 12 weeks with ribavirin or 24 weeks without ribavirin is recommended.

This is an alternative regimen, because of safety issues (in people with decompensated cirrhosis, it can cause liver failure and death); propensity for drug–drug interactions with HIV antiretrovirals and other medicines; the requirement for genotype 1 subgenotyping and resistance testing in genotype 1a; and because it is effective only against infections with genotypes 1 and 4.

Dosing: 150 mg once daily

WHO Model List of Essential Medicines. Simeprevir is included in the nineteenth edition of the WHO EML *(21)* published in April 2015, and in the thirteenth invitation to submit an EOI for product evaluation in the WHO Prequalification Programme.

Patents. The WHO report on the patent situation of simeprevir comprises 12 patent families for simeprevir, including the primary patent claiming the base compound, which is likely to constrain generic competition where granted. The primary patent has been widely filed, including in ARIPO and OAPI, and many other LMICs. *See* for further details http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)* and Table 3.1.

Registration. Simeprevir is registered in a few middle-income countries, including Brazil, Bulgaria, Colombia, Egypt, El Salvador, Guatemala, Lebanon, Mexico, Moldova, Nicaragua, Peru, Romania, Thailand and Ukraine, and in one low-income country (Rwanda). The originator company has not applied for WHO prequalification.

Pricing and access. Simeprevir is mainly used in high-income countries. In the US, it was launched at US$ 66 360 for a 12-week treatment course. Local access prices have been agreed with Brazil, Egypt and Indonesia. In these agreements, the prices are significantly lower than in high-income countries bur vary across middle-income countries from US$ 250 in Egypt, US$ 400 in Indonesia, US$ 866 Brazil and up to US$ 9431 in Romania for a 28-day supply of simeprevir.

Janssen has not announced any access programme for simeprevir. The company has not entered into a license agreement, despite the fact that simeprevir has already been on the market for nearly three years. It informed WHO that it is “planning on working on a voluntary licensing agreement with generic manufacturers”, but that the company has “no active interest from the Medicines Patent Pool at this point”. It will evaluate requests for compassionate use from any country where simeprevir is not available. There is no generic production of simeprevir at this time, but two generic manufacturers (Incepta in Bangladesh and Hetero in India) reportedly plan to develop a generic version.

5.4. Sofosbuvir

General information

Therapeutic class: HCV nucleotide polymerase inhibitor

Originator company: Gilead Sciences

First approval on 22 November 2013 (EMA)

2016 WHO Guidelines

Preferred regimen: sofosbuvir-based regimens are recommended for all HCV genotypes in people with or without cirrhosis. The WHO guidelines recommend the use of sofosbuvir with ribavirin, sofosbuvir with daclatasvir (with or without ribavirin) and the FDC of sofosbuvir/ledipasvir with or without ribavirin.

Alternative regimen: sofosbuvir plus simeprevir is an alternative regimen for infection with HCV genotypes 1 and 4, and sofosbuvir is included in an alternative regimen for infection with HCV genotypes 5 and 6, with pegylated interferon and ribavirin.

WHO Model List of Essential Medicines. Sofosbuvir is included in the nineteenth edition of the WHO EML *(21)* published in April 2015 and was included in the WHO prequalification programme.

Patents. The WHO report on the patent situation of sofosbuvir comprises 14 different patent families out of the large number of patents filed and covering different aspects of sofosbuvir. The patents cover the compound, the prodrug, crystalline forms, formulations and combinations. The primary patents that claim the compound and the prodrug have not been filed in certain countries or regions (*see* http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)* and Table 3.1). Secondary patents have been filed more widely and thus require screening as to what extent they are relevant to local production or importation of generic versions. NGOs and competitors have filed a number of patent oppositions in different jurisdictions, and different patent applications have been rejected in ARIPO, Egypt, Ukraine and other countries. Most of these countries are also included in the territory of the license agreement. *See* for further details http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/ *(26)* and Table 3.1.

Registration. Information about the registration status of sofosbuvir is available online *(77, 95)*. The innovator company announced that it endeavours to register its hepatitis products in all countries included in its access programme (101 countries) using the royalties of the license agreements to finance this activity.

Sofosbuvir has been registered in many high-income countries, including Argentina, Chile, Uruguay and Venezuela, as well as in a number of LMICs: Bolivia, Brazil, Bulgaria, Dominican Republic, Egypt, El Salvador, Georgia, India, Indonesia, Mexico, Mongolia, Pakistan, Peru, the Philippines, Romania, Thailand, Ukraine, and one low-income country, Rwanda. Registration for sofosbuvir is pending in 11 other LMICs, eight of which are in the licensed territory.

WHO Prequalification. None of the generic formulations produced by the different companies has been prequalified or approved by a stringent regulatory authority. Seven generic products and four API manufacturers have entered the official phase of WHO prequalification; *see* section 3.3 for more details.

TABLE 5.2. Status of registration of generic sofosbuvir 400 mg, reported by generic companies

Company	Approved	Submitted	Dossier in preparation
Hetero	Algeria, Bangladesh, Democratic Republic of the Congo, Egypt, India, Nepal	Kenya, Benin, Myanmar, Viet Nam	19, including Ukraine
Natco	Kyrgyzstan, Nepal	36 countries	
Strides		20 countries including Egypt, Nigeria, South Africa	
Pharco	Azerbaijan, Egypt, Kyrgyzstan and Ukraine		
Cadila		India	
Pharma 5	Côte d'Ivoire, Guinea, Morocco		
Incepta			24 countries
Richmond	Argentina		
Getz Pharma	Pakistan		

Pricing and access. In the USA, sofosbuvir was launched in 2013 at US$ 1000 per pill, or US$ 28 000 for a 28-day supply. Since then, the price has declined through negotiations with medicines distributors and public sector agencies such as the U.S. Veterans Administration. The high price has led public and private payers in high-income countries to institute non-evidence-based access restrictions – including for those with a history of current or past injection drug use. Prices in high-income countries remain high and put serious pressure on health systems (*see* Chapter 3).

In countries that are not included in the voluntary license agreement and in high-income countries, the innovator company, Gilead Sciences, negotiates prices on a country-by-country basis without disclosing the negotiated price publicly. In Brazil, the price of sofosbuvir was negotiated at US$ 2292 for a 28-day supply; after a joint negotiation between the company and the Mercosur countries and their Associate States, all of them were offered the same price as Brazil (except Argentina, as shown in Table 4.1) *(83)*. In Romania, sofosbuvir costs US$ 16 368 for a 28-day supply.

The voluntary licensing agreement of the innovator company covers 101 LMICs. It includes the sofosbuvir/ledipasvir FDC and the sofosbuvir/velpatasvir FDC. The innovator company has signed agreements with 11 generics manufacturers in India, two generics manufacturers in Egypt and one manufacturer in Pakistan. The latter agreements allow them to import or manufacture and sell sofosbuvir in their national markets; *see* Chapter 3 for more detail.

Licensees cannot export their finished product or APIs to countries where patents have been awarded or are pending. Countries where no patents are in force can, however, buy sofosbuvir or sofosbuvir/ledipasvir from manufacturers that have not signed the license agreement with Gilead Sciences.

The 101 countries in the territory include all low-income and many but not all middle-income countries. The agreement does not include several middle-income countries with a high HCV prevalence, including Brazil (1.9 million), China (8.9 million), Mexico (0.9 million), Thailand (0.9 million) and Ukraine (0.9 million) (*see* Chapter 3 for further details on the license agreement). These countries can buy from the 11 Indian licensees or directly from Gilead Sciences, which

offers sofosbuvir for US$ 300 for a 28-day supply to all countries included in the agreement under its differential pricing scheme. Reported prices of sofosbuvir in the local Indian market vary from US$ 169 to US$ 338. Generics producers offer sofosbuvir at much lower prices, down to US$ 51 per month in Egypt's public sector and US$ 15 in Pakistan. A few companies quoted prices for exporting sofosbuvir: Cipla US$ 233/28-day supply; Hetero US$ 250–300/28-day supply; Natco US$ 199/28-day supply; Pharco US$ 60 and US$ 76/28-day supply (for the public and private sectors, respectively), and Strides Shasun for US$ 300/28-day supply (Tables 5.3 and 5.4). Table 5.5 gives a list of companies that produce the API of sofosbuvir.

Anti-diversion measures. To access the reduced prices offered by Gilead Sciences and its licensees, countries must implement Gilead Sciences' anti-diversion measures; so far, this has been documented in Egypt, Georgia, Pakistan, Romania and Rwanda. It is important that such programmes do not compromise patient autonomy, confidentiality, the patient–medical provider relationship, and do not logistically complicate procurement and delay treatment scale up (*see* Chapter 4, Box 4.2).

TABLE 5.3. Prices of generic sofosbuvir 400 mg, per 28-day supply, reported from Bangladesh Egypt, India *(64)*, Morocco and Pakistan

Manufacturers	Marketing companies/ Distributors	Country	Local market		Export	
			Public	Private	Public	Private
Incepta Pharmaceuticals Ltd.	Incepta Pharmaceuticals Ltd.	Bangladesh	N/A	$197	N/A	N/A
Pharco*	Pharco*	Egypt	$51	$70	$70–85	N/A
Natco Pharma Ltd.	Natco Pharma Ltd	India	N/A	$149	N/A	$199
	Emcure Pharmaceuticals Ltd		N/A	$154	N/A	N/A
	Mylan Ltd		N/A	$163	N/A	N/A
	Strides Shansun		N/A	$108	N/A	$300
	Zydus Heptiza (division of Cadila Healthcare Ltd)		N/A	$185	N/A	N/A
Hetero Labs	Hetero Labs		N/A	$185	N/A	$250–$300
	Abbott India Ltd		N/A	$192	N/A	N/A
	Biocon		N/A	$215	N/A	N/A
	Cipla Ltd		N/A	$169	N/A	$233
	Dr Reddy's		N/A	$215	N/A	N/A
	Ranbaxy		N/A	$154	N/A	N/A
	Sun Pharmaceuticals Ltd		N/A	$180	N/A	N/A
Pharma 5	Pharma 5	Morocco	N/A	$300	N/A	N/A
Getz Pharma	Getz Pharma	Pakistan	N/A	$15–42	N/A	N/A

*26 other manufacturers or distributors are currently producing or marketing generic sofosbuvir in Egypt.
Note: All prices in US dollars. Indian prices based on the exchange rate of US$ 1=65 Indian Rupees *(64)*
N/A: not available

TABLE 5.4. Companies that produce or market sofosbuvir 400 mg

Distributor	Manufacturer of the finished formulation	Type of license with Gilead Sciences	Country of origin
Companies with a VL from Gilead			
Hetero[1]	Hetero	International	India
Biocon	Hetero	International	India
Cipla	Hetero	International	India
Sun Pharma	Hetero	International	India
Natco[1]	Natco	International	India
Cadila	Natco	International	India
Mylan	Natco	International	India
Strides Shasun	Natco	International	India
Companies with a national VL from Gilead			
Pharmed Healthcare	Gilead	In-country	Egypt
Magic Pharma	Gilead	In-country	Egypt
Ferozsons	Gilead	In-country	Pakistan
Companies outside of the Gilead VL			
Richmond	Richmond	N/A	Argentina
Incepta	Incepta	N/A	Bangladesh
Beximco	Beximco	N/A	Bangladesh
Pharco	Pharco	N/A	Egypt
Abbott India Ltd.	Hetero	N/A	India
Dr Reddy's	Hetero	N/A	India
Emcure	Natco	N/A	India
Pharma 5	Pharma 5	N/A	Morocco
Getz Pharma	Getz Pharma	N/A	Pakistan

[1] Hetero and Natco market sofosbuvir under their own name, but also sell finished formulation to other companies.

TABLE 5.5. Companies that produce the active pharmaceutical ingredient for sofosbuvir 400 mg

Company	Type of license	Country
Companies producing with a Gilead VL		
Laurus	International	India
Sequent	International	India
Hetero	International	India
Companies producing without a Gilead VL		
CAD Middle East Pharmaceutical industries LLC	None	Saudi Arabia
Pharco	None	Egypt
Xiamen Halogenetics Biotechnology Ltd	None	China

Note: 26 other manufacturers or distributors are currently producing or marketing generic sofosbuvir in Egypt.

5.5. Sofosbuvir/ledipasvir

General information

Therapeutic class: FDC of a nucleotide polymerase inhibitor and an NS5A inhibitor

Originator company: Gilead Sciences

First approval on 10 October 2014 (US FDA)

2016 WHO Guidelines

Preferred regimen: sofosbuvir/ledipasvir is recommended for infection with HCV genotypes 1, 4, 5 and 6 in people with or without cirrhosis. The WHO guidelines recommend the use of sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks.

WHO Model List of Essential Medicines. Sofosbuvir/ledipasvir is included in the nineteenth edition of WHO EML *(21)* published in April 2015, and in the thirteenth invitation to submit an EOI for product evaluation in the WHO Prequalification Programme.

Patents. The WHO Report on the patent situation of ledipasvir *(26)* lists seven different patent families for ledipasvir with the primary patent covering the compound WO2010132601 being the most important one for generic competition. This patent has been widely filed, including in the two regional African patent offices, ARIPO and OPAI. Table 3.1 provides an overview of the patent situation in the countries included in the WHO patent reports. Most of the countries where the primary patent has not been filed or granted are included in the territory of the license agreement, for example, the Philippines, but there are also some countries outside the license agreement, for example, Georgia, Iran, Jordan and Malaysia. Secondary patents can be relevant, in particular, where they cover relevant combinations of DAAs (*see*, for example, Patents 5 and 6 in WHO Patent situation of key products for treatment of hepatitis C, updated June 2016 – ledipasvir and the report on sofosbuvir *(26)* and Tables 3.1 and 3.2).

Registration. Information about the registration status of sofosbuvir/ledipasvir of the originator company is available online *(77)*. The company announced that it endeavours to register its hepatitis products in all countries included in its access programme (101 countries) using the royalties of the license agreements to finance this activity. Sofosbuvir/ledipasvir has been registered in eight LMICs: Egypt, Ethiopia, Georgia, Mexico, Mongolia, Morocco, Rwanda, Tunisia and Uruguay. Registration for sofosbuvir/ledipasvir is pending in 12 other LMICs, nine of which are in the licensed territory.

WHO Prequalification. For the time being, none of the generic formulations available from different companies has undergone approval by a stringent regulatory authority or prequalification. Several generics companies plan to apply for WHO prequalification for their versions.

Pricing and access. Sofosbuvir/ledipasvir is covered by the same voluntary licensing agreement as sofosbuvir (*see* Chapter 3 for details).

The 101 countries included can purchase generic sofosbuvir/ledipasvir from the 11 Indian licensees or buy sofosbuvir/ledipasvir for US$ 400 per 28-day supply from the originator company under its differential pricing scheme. Several generics companies reported offering the combination at prices ranging from US$ 250 to US$ 450 per 28-day supply, either producing or marketing sofosbuvir/ledipasvir (Tables 5.6 and 5.7). Table 5.8 gives the companies that produce the APIs for sofosbuvir/ledipasvir.

TABLE 5.6. Price of generic sofosbuvir/ledipasvir 400 mg/90 mg in selected countries

Country (generics suppliers)	Sector	Price range, US$, per 28-day supply
India (Cadila, Hetero, Natco, Sun Pharma)	Public	250–400
	Private	450
Bangladesh (Incepta)	Private	353

TABLE 5.7. Companies that produce or market sofosbuvir/ledipasvir 400 mg/90 mg

Distributor	Manufacturer of the finished formulation	Type of license agreement	Country of origin
Companies selling or producing finished formulations of sofosbuvir/ledipasvir with a license from Gilead Sciences (101 countries/territories)			
Hetero[1]	Hetero	International	India
Cipla	N/A	International	India
Sun Pharma	Hetero	International	India
Natco[1]	Natco	International	India
Cadila	Hetero	International	India
Mylan	N/A	International	India
Companies selling or producing finished formulations with a national license			
None reported			
Companies selling or producing finished formulations of sofosbuvir/ledipasvir without a Gilead license			
Incepta	Incepta	None	Bangladesh
Beximco	Beximco	None	Bangladesh
Pharmed Health Care, Future Pharmaceutical Industries, Marcyrl co., Organo Pharma, Averroes Pharmaceuticals	N/A	None	Egypt

[1] Hetero and Natco market sofosbuvir/ledipasvir under their own names, but also sell finished formulation to other companies.

TABLE 5.8. Companies that produce the active pharmaceutical ingredients for sofosbuvir/ledipasvir 400 mg/90 mg

Company	Type of license	Country
Companies producing under the Gilead license		
Laurus	International	India
Hetero	International	India
Companies producing without a Gilead license		
CAD Middle East Pharmaceutical industries LLC	None	Saudi Arabia
Pharco	None	Egypt
Xiamen Halogenetics Biotechnology Ltd.	None	China

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