World Health Organization

PROGRESS REPORT ON ACCESS TO HEPATITIS C TREATMENT

FOCUS ON OVERCOMING BARRIERS IN LOW- AND MIDDLE-INCOME COUNTRIES

MARCH 2018

A patient holds her hepatitis C medicines at the MSF hepatitis C clinic at Preah Kossamak Hospital in Phnom Penh, Cambodia

CREDIT: TODD BROWN

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ABBREVIATIONS

API	active pharmaceutical ingredient
BMS	Bristol-Myers Squibb
CHAI	Clinton Health Access Initiative
DAA	direct-acting antiviral (medicine)
DCV	daclatasvir
DND*i*	Drugs for Neglected Diseases *initiative*
D+o/p/r	dasabuvir + ombitasvir/paritaprevir/ritonavir
EMA	European Medicines Agency
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HCV	hepatitis C virus
HIC	high-income country
HIV	human immunodeficiency virus
LDV	ledipasvir
LIC	low-income country
LMIC	lower-middle-income country
MoH	Ministry of Health
NGO	nongovernmental organization
OECD	Organisation for Economic Co-operation and Development
RDV	ravidasvir
RNA	ribonucleic acid
SMV	simeprevir
SOF	sofosbuvir
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UN	United Nations
UMIC	upper-middle-income country
USA	United States of America
US FDA	United States Food and Drug Administration
VEL	velpatasvir

Hepatitis C screening in Cairo, Egypt
CREDIT: WHO EGYPT

WHO promotes and supports country efforts to achieve universal access to affordable HCV treatment based on the WHO *Global health sector strategy on viral hepatitis, 2016–2021*, which Member States adopted in 2016.

EXECUTIVE SUMMARY

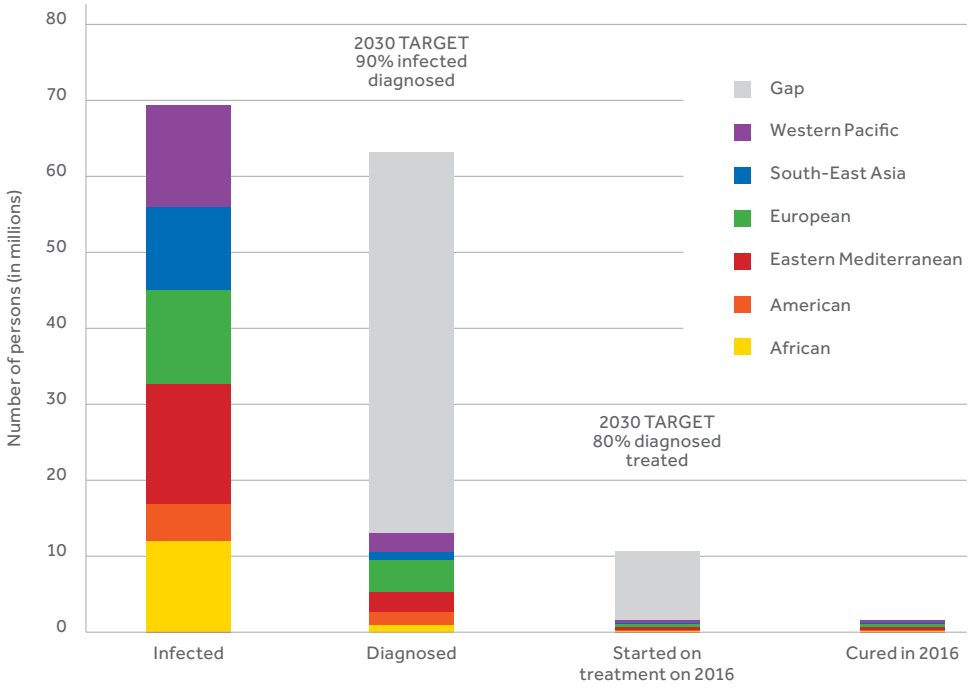
UPTAKE OF DIRECT-ACTING ANTIVIRALS IS INCREASING SLOWLY AND UNEVENLY

Increased access to highly effective direct-acting antivirals (DAAs) for the treatment of infection with the hepatitis C virus (HCV) is revolutionizing the prospect of ending HCV epidemics. Globally, the number of people who initiated DAA-based treatment for HCV rose between 2015 and 2016, from approximately 1 million to 1.5 million. A small number of countries were responsible for the bulk of that increase. **Egypt** and **Pakistan** accounted for about half of all people who started DAA treatment in 2016. There was encouraging progress also in countries as diverse as **Australia**, **Brazil**, **China**, **France, Georgia**, **Mongolia, Morocco, Rwanda** and **Spain.**

EXPANDING ACCESS TO TREATMENT: CHALLENGES AND OPPORTUNITIES

Access to treatment needs to expand at a much quicker pace. The majority of the estimated 71 million people living with HCV remain untreated (Fig. 1). Much more equitable access to DAAs for people with chronic HCV infection is necessary if the WHO target of eliminating HCV as a major public health threat by 2030 is to be achieved. Reaching the 2030 target will require diagnosing 90% of people living with HCV and treating 80% of diagnosed people with DAAs, along with drastically reducing new HCV infections.

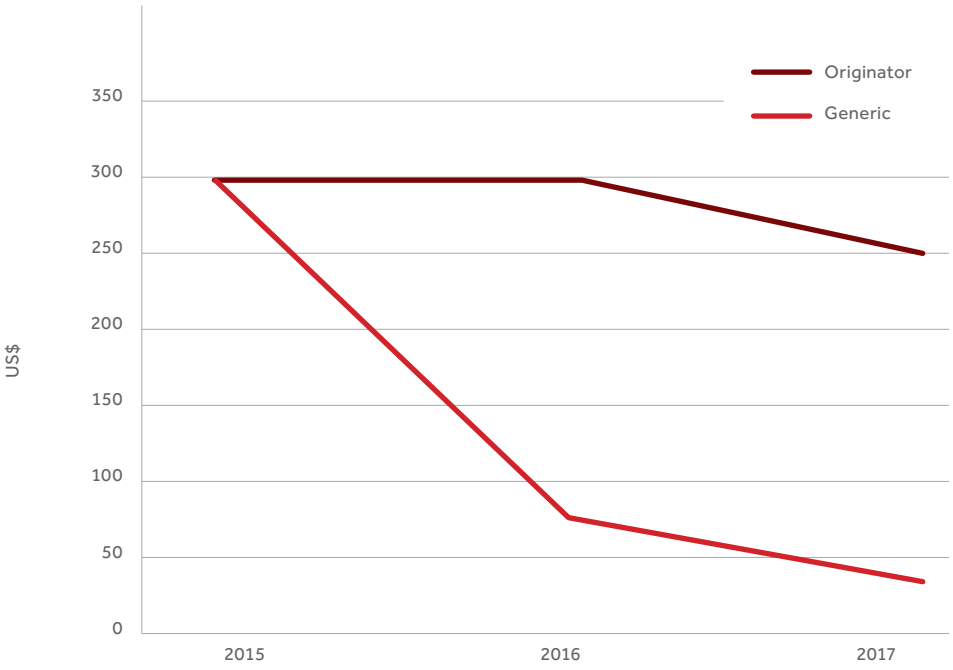
Fig. 1. Cascade of care for people living with HCV infection, by WHO region, 2016



Increased competition has driven down treatment prices…

Driving increased access to DAA-based treatment is the steep price reductions that were achieved since 2015 (Fig. 2), which are due largely to increased competition, especially from generic manufacturers. The issuing of voluntary licenses covering more than 100 countries for some of the recommended DAAs enables those countries to procure generic DAAs from the licensees. The absence of patents for some DAAs in certain countries has allowed generic manufacturers to set up local production without a license and allows those manufacturers to export to other countries where there are no patents. Overall, more than 60% of people with HCV infection now live in countries that could procure more affordable generic DAAs (Fig. 3), making it possible to implement transformative treatment programmes. However, not all countries have yet seized the opportunity to initiate and scale up treatment programmes and to benefit from access to more affordable generic DAAs.

Fig. 2. Lowest prices for sofosbuvir reported by originator and generic companies in low- and lower-middle-income countries, per 28-day supply, 2015–2017



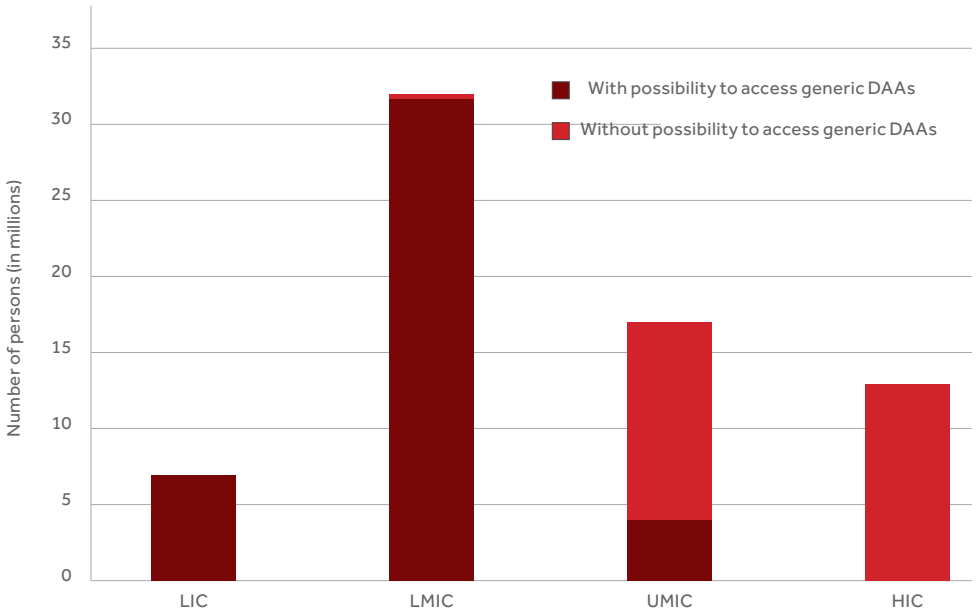
The appendix on drug profiles presents updated data on innovator and generic DAA availability, registration status and prices for all recommended DAAs.

… but costs remain unaffordable in many upper-middle- and high-income countries

In comparison to those countries where generics are available, prices of DAAs in upper-middle-income and high-income countries remain high, impeding equitable access to safe and effective treatment.

As Fig. 3 shows, countries that lack access to generic DAAs are almost exclusively in the upper-middle-income and high-income categories, which are typically not included in the license agreements, and represent about 38% of people living with HCV globally. They include, for example, **Brazil**, **China**, **Colombia**, **Kazakhstan**, **Mexico** and **Turkey**, which together are home to about 14 million people living with HCV infection.

Fig. 3. Number of people living with HCV with possibility to access generic DAAs, by country income group, 2017



HIC: high-income countries; LIC: low-income countries; LMIC: lower-middle-income countries; UMIC: upper-middle-income countries

Coverage of screening and diagnostic services remains too low

Despite progress since 2014, the majority of people living with HCV worldwide are still not diagnosed and therefore remain untreated. Globally, only about one in five people living with HCV in 2016 had been diagnosed. In low-income countries, less than 10% of people infected with HCV had been diagnosed, compared with over 40% in high-income countries. Diagnostic services need to reach much larger numbers of people living with HCV.

The cost of HCV testing continues to be a hurdle, not least because it often involves out-of-pocket payment. While prices of rapid diagnostic tests have fallen as low as US$ 1, confirmatory tests still cost US$ 15–100, depending on the product and country. Affordable, one-step, point-of-care testing would make it possible to identify much larger numbers of people in need of treatment. Annex 1 presents pricing data for the most current diagnostics.

Treatment options have increased

DAA therapy options continue to increase and improve. Eleven DAA regimens (five single-component DAAs and six fixed-dose combinations) have received regulatory approval from at least one stringent regulatory authority since 2013.

Since the publication of the 2016 WHO *Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection*, three pangenotypic regimens that are effective across all six major HCV genotypes (sofosbuvir/velpatasvir; sofosbuvir/velpatasvir/voxilaprevir; and glecaprevir/pibrentasvir) have been approved by the United States Food and Drug Administration and the European Medicines Agency. This heralds a major breakthrough for HCV treatment. These regimens greatly reduce the need for costly genotyping and simplify both the procurement and delivery of DAAs. However, access in low- and middle-income countries is still limited. The sofosbuvir/velpatasvir regimen has been registered for use in only three low- and middle-income countries, while the originator of the glecaprevir/pibrentasvir regimen is yet to announce an access programme for low- and middle-income countries. The triple DAA regimen (sofosbuvir/velpatasvir/voxilaprevir) is registered for use only for retreatment of people with HCV infection who previously failed a DAA regimen.

TOWARDS UNIVERSAL COVERAGE – WHAT IS NEEDED?

Countries have different needs and face different realities as they confront their HCV epidemics. While some are still struggling with price and patent barriers, other countries are able to move on. This reports describes country responses for expanding access to HCV treatment in a number of selected countries.

The analysis of country experiences shows that, while access to affordable treatment is key, countries need a strong government response, national plans for preventing, diagnosing and treating HCV, and adequate financing to roll out and sustain HCV services. Stringent quality assurance of DAAs is also necessary, along with effective regulatory processes. (*See* Table 4.1. Summary of country responses for expanding access to HCV treatment, mid-2017.)

Strong national responses are needed

Treatment expansion has accelerated in countries that have mobilized a strong government response – as seen in **Australia**, **Brazil, Egypt** and **Mongolia**, for example. This enables them to develop national treatment plans, mobilize and allocate resources accordingly, and pursue supportive arrangements that can improve access to treatment, such as regulatory actions, price negotiations, and integration of laboratory, procurement and supply management processes into broader health systems. While many low- and middle-income countries can now access more affordable generic DAAs, to date only a few have prioritized hepatitis treatment and integrated the necessary services within their health systems.

Support for civil society organizations and collaboration with them can bolster government responses and increase the scope and acceptability of HCV programmes, as seen in **Cambodia** and **Ukraine**, for example. This is especially important for reaching and prioritizing the diagnosis and treatment of at-risk populations, such as people who inject drugs, prisoners and men who have sex with men. It is also important to remove legal and institutional barriers that impede people's access to HCV screening and treatment services.

Market competition will lead to reduced prices

The WHO survey data show clearly that the most affordable DAA prices are available in countries where generic competition is strong. Competition could be intensified by expanding voluntary license agreements or by establishing new license agreements with the Medicines Patent Pool, particularly for pangenotypic treatment combinations. Companies that have not signed license agreements should enter into negotiations with the Medicines Patent Pool. Countries that cannot achieve affordable prices, for example, through price/volume agreements or pooled procurement schemes, such as the revolving fund of the Pan American Health Organization, can use flexibilities enshrined in the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), as was done by **Malaysia**.

Greater market transparency would facilitate price cuts

Countries that try to negotiate reduced prices with manufacturers require market intelligence on what other countries and buyers are paying. This report includes updated information on DAA prices and registration collected from a selection of countries (*see* Table 4.2) and a summary of procurement data for all recommended DAAs from innovator and generic companies (*see* Appendix. Drug profiles). Overall, price transparency for DAA regimens, particularly for high-income countries, remains inadequate, hindered by confidentiality agreements.

Increased financing options should be sought

To achieve HCV treatment targets, financing will need to increase and, in most countries, those increases will have to come from domestic sources as part of a broader push towards universal health coverage. Unlike for HIV, tuberculosis or malaria, international solidarity is still largely lacking in the viral hepatitis response. For most countries, this is unlikely to change dramatically in the foreseeable future. Demonstrated programme efficiencies and solid investment cases would strengthen calls for increased public financing of HCV treatment services. Integrating HCV treatment into national health benefit packages, expanding insurance coverage and reducing out-of-pocket expenditures remains key to increasing access to treatment.

Quality assurance and registration of medicines and diagnostics are needed

Originator and generic manufacturers should seek WHO prequalification for their HCV products, so countries can procure from a range of quality-assured diagnostic and treatment options. As of February 2018, WHO had prequalified the sofosbuvir tablets from three generic companies, as well as daclatasvir tablets of the originator company. The majority of generic DAAs, however, are neither WHO prequalified (largely because producers have not applied for prequalification) nor authorized by a stringent regulatory authority.

If a DAA is not registered in a country, it can significantly delay or impede the availability of the regimen. Despite an increase in the number of countries that have approved generic and/or originator DAA regimens, DAAs have been registered in only a minority of low- and middle-income countries. In 2017, at least one originator or generic version of sofosbuvir was registered in 56 low- and middle-income countries and for daclatasvir, at least one originator or generic version was registered in 23 low- and middle-income countries. If registrations increase, the procurement choices would broaden, which would also enable countries to streamline their procurement and achieve lower prices.

METHODOLOGY

This report updates the first edition, published in 2016, and reviews the progress countries have made in expanding access to life-saving DAAs. It draws on a WHO survey on the availability and use of DAAs in 23 low- and middle-income countries across six regions and a survey of innovator and generic companies (both conducted between March and December 2017), as well as interviews with key informants and stakeholders, and other new hepatitis C treatment-related data. The report reviews the main challenges countries face and describes recent developments in relation to five key factors that determine access to DAA medicines: affordability, quality assurance, regulatory approval, government commitment and financing. It highlights key areas for action by ministries of health and other government decision-makers, pharmaceutical manufacturers and technical partners.

WHAT WHO IS DOING TO SUPPORT ACCELERATED DAA SCALE UP

WHO promotes and supports country efforts to achieve universal access to affordable HCV treatment based on the WHO *Global health sector strategy on viral hepatitis, 2016–2021*, which Member States adopted in 2016.

WHO is assisting an increasing number of countries in drafting and implementing national testing and treatment policies. A WHO *Manual for the development and assessment of national viral hepatitis plans: a provisional document* is also available to support country planning.

Since 2015, the number of countries with comprehensive national plans and strategies on hepatitis has increased sharply. By November 2017, 84 of 139 reporting countries had developed such plans, an almost fivefold increase since 2012. Several countries have shifted to more ambitious national strategies, including **Brazil,** which has broadened treatment eligibility, and **Egypt, Georgia**, **Mongolia** and **Morocco** – all of which are aligning their programmes to reach the WHO target of eliminating HCV by 2030.

WHO provides technical assistance to countries for scaling up treatment and addressing price- and intellectual property-related barriers. For example, a consultation held at the WHO Regional Office for the Western Pacific in August 2017 on access to hepatitis medicines in upper-middle- and high-income countries enabled countries and experts to discuss prospective strategies for increasing access. WHO has also commissioned estimates of the cost of producing medicines included on the WHO *Model list of essential medicines*, which will be published in 2018, and has published the patent situation of key DAAs.

WHO reviews all new HCV treatments for consideration for inclusion in the WHO *Model list of essential medicines*, and will keep the list updated to provide guidance to procurement programmes and to facilitate access to affordable treatments. It has expanded its prequalification programme to promote quality assurance of new DAAs and increase the availability of quality-assured medicines and diagnostics. As of February 2018, WHO had prequalified three DAAs from generic manufacturers and one from an originator company, while a further three manufacturers have filed submissions. WHO has also prequalified two rapid diagnostic tests for HCV antibodies and an HCV ribonucleic acid (RNA) assay that allows for confirmation of chronic HCV infection even in remote areas.

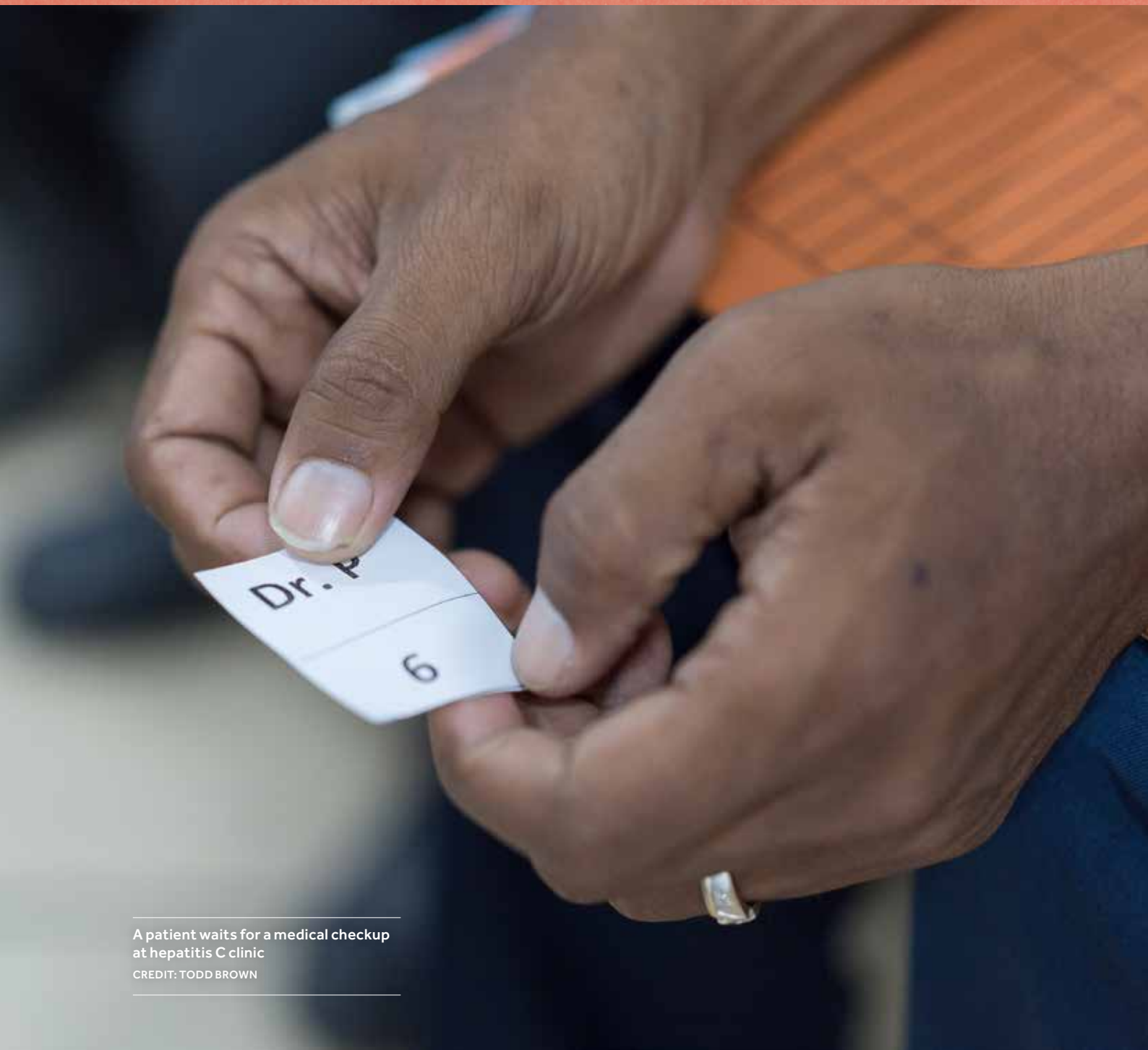
In this rapidly developing field, WHO will release updated HCV care and treatment guidelines in 2018 to promote the transition to newer, more effective medicines, particularly pangenotypic DAA regimens that are effective against all six major genotypes of HCV. In addition, WHO is moving towards recommending HCV treatment for all individuals diagnosed with HCV infection, regardless of disease stage (except for pregnant women and children under the age of 12 years). WHO proactively supports countries in adapting testing and treatment guidelines to the respective country context and in implementing these guidelines.

In addition to normative guidance, quality assurance and technical support to countries, WHO documents the status of the HCV response, trends in access to and use of DAAs, and new developments related to prices, registration, intellectual property rights and procurement of DAAs. Those updates are published regularly in a global report on access to hepatitis C treatment, of which this report is the second edition.

WHO uses its convening mandate to promote a stronger global response to HCV epidemics. In November 2017, WHO and the World Hepatitis Alliance co-organized the second World Hepatitis Summit, together with the Government of Brazil, in São Paulo, Brazil. The São Paulo Declaration on Hepatitis (issued by national governments) recognized the importance of health systems strengthening for achieving universal health coverage, with an emphasis on populations that are most affected and at high risk of infection. The Declaration also highlighted the need to mobilize adequate resources for the viral hepatitis response, especially in low- and middle-income countries, and to improve equitable access to safe and effective treatment for HCV infection.

1

INTRODUCTION



A patient waits for a medical checkup at hepatitis C clinic

CREDIT: TODD BROWN

Globally, 1.76 million people received treatment for infection with the hepatitis C virus (HCV) in 2016.[a] The majority of people who started treatment in 2016 (about 86%) received direct-acting antivirals (DAAs), which have a cure rate of over 95%. Combined with the 1.1 million people who started treatment in 2015, this brought to almost 3 million the number of people who accessed HCV therapy in 2015–2016. The expansion of treatment access needs to accelerate, however. Of the approximately 71 million people living with HCV,[b] only a small minority was able to access curative treatment in 2016.

This report reviews access to HCV treatment, focusing on low- and middle-income countries. As an update to the first edition, published in 2016 *(1)*, it documents changes in the regulatory, production, procurement and programming factors that determine access to DAA medicines, and reports on progress made in countries in expanding treatment access. The report draws on extensive quantitative and qualitative data collected from 23 low- and middle-income countries with major hepatitis C epidemics (Box 1), which together account for more than two thirds of all HCV infections globally.

BOX 1. METHODS AND DATA SOURCES

Much of the data presented in this report are drawn from surveys that WHO conducted among selected countries and from information received from pharmaceutical companies between March and December 2017, and other new data on hepatitis C treatment up to end 2017. Representatives of ministries of health were requested to complete questionnaires regarding the status of registration, importation, price and production of generic versions of DAAs and of HCV treatment uptake. Countries were selected to represent different geographical regions, country income levels and hepatitis C prevalence, and illustrate different approaches to enhancing access to affordable DAA medicines. The 23 selected countries were: Argentina, Brazil, Cameroon, China, Egypt, Georgia, India, Indonesia, Malaysia, Morocco, Myanmar, Nigeria, Pakistan, the Philippines, Romania, Russian Federation, Rwanda, South Africa, Thailand, Ukraine, Uzbekistan and Viet Nam.

Questionnaires regarding pricing, licensing and regulatory status were also sent to four originator and thirty generic DAA-producing companies. Excluding non-responses and manufacturers that declined to answer or sent incomplete answers, a total of three originator and 13 generic manufacturers were considered for this report. Inclusion of suppliers does not imply any judgement about the quality of the products. Twenty-seven representatives of selected nongovernmental organizations (NGOs) and experts from country programmes and academic institutions were also interviewed regarding global- and country-level activities for improving access to DAAs (*see* the Acknowledgments section). Data were collected from May 2017 to September 2017.

While WHO is responsible for drafting 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 MedsPaL *(2)*, the regularly updated patent database of the Medicines Patent Pool and the WHO patent reports as published in June 2016.

The report focuses on access to HCV medicines (DAAs). Since the data are very limited on the different models of service delivery used in countries to increase access to DAAs, issues such as task-shifting and decentralized services for pangenotypic DAA regimens are not covered in this report. Those issues will be addressed in future treatment access reporting.

Estimates of the prevalence of HCV infection in countries are based on calculations done by the Center for Disease Analysis and were previously published in the 2017 WHO *Global hepatitis report (3)*. The update of global HCV diagnosis and treatment uptake data for 2016 used the same methods as those reported in the 2017 *Global hepatitis report* and were presented by WHO at the World Hepatitis Summit 2017 *(4)*.

a Global estimates for 2017 were being finalized when this report went to press.
b This estimate is for 2015; an updated estimate for 2016, validated by countries, will be published in early 2018.

2

STATUS OF THE HEPATITIS C TREATMENT RESPONSE

People waiting to receive free hepatitis C testing during World Hepatitis Day 2016 campaign event in Kigali, Rwanda

CREDIT: WHO RWANDA

2.1 MORE PEOPLE ARE RECEIVING CURATIVE HCV TREATMENT

About 86% of those who started HCV treatment in 2016 received DAAs. In 2017, treatment access increased further as several low- and middle-income countries continued to roll out DAA therapy, notably **Egypt,** which alone accounted for almost 40% of people who started HCV treatment globally in 2016; other countries included **Brazil**, **China**, **Georgia** and **Pakistan**. Achievements in these countries are described below in descending order of the number of people started on treatment.

- **Egypt**'s comprehensive national testing and treatment programme and domestic production of low-cost generic DAAs has enabled rapid treatment scale up, with the number of people receiving DAAs rising from 30 000 in 2014 to 700 000 in 2016. By September 2017, a cumulative total of 1.5 million people had received HCV treatment.
- In **China,** a total of approximately 200 000 people had been treated as of mid-2017.
- **Pakistan** showed progress, with 161 000 people receiving treatment in 2016 (mostly through the private sector) compared with 65 000 in 2015.
- **Brazil's** HCV programme is growing, with more than 41 000 people having received treatment in 2016, up from about 7500 in 2015.
- In **Georgia**, more than 21 000 people received treatment in 2016 compared with less than 6000 in 2015.
- In **Morocco**, approximately 6500 people received treatment in 2016 (almost entirely in the private sector), compared with only 100 in 2015.
- **Mongolia** had treated more than 6500 people in 2016, within 20 months of setting up its HCV treatment programme.
- Elsewhere, among countries that provided treatment data,[c] there have been small increases in uptake in, among others, **Romania** (6000 persons received DAA treatment in 2016), **Ukraine** (2500 persons in 2016 compared with 2000 in 2015) and **Rwanda** (1000 persons in 2016 compared with 300 in 2015).

BOX 2. A BRIEF OVERVIEW OF THE HEPATITIS C EPIDEMIC

In 2015, an estimated 71 million people globally were living with HCV infection and the epidemic was responsible for an estimated 400 000 deaths, primarily due to liver cancer and cirrhosis *(3)*.[d] The introduction of daily, single-tablet curative treatment for HCV since 2014 has revolutionized the prospects of ending HCV epidemics.

Low- and middle-income countries accounted for about 75% of people living with HCV globally in 2016, with the other 25% residing in high-income countries. The Center for Disease Analysis estimates that **China** has the largest HCV epidemic (almost 10 million people living with HCV in 2015), followed by **Pakistan** (7.2 million), **India** (6.2 million) and **Egypt** (5.6 million) *(5)*. These four countries account for almost 40% of all people living with HCV *(5)*. Unsafe health-care procedures and injection drug use continue to be the leading causes of new HCV infections worldwide.

The countries accounting for 80% of global viraemic HCV infections were (listed according to the size of their epidemics): China, Pakistan, India, Egypt, Russian Federation, United States of America, Nigeria, Brazil, Democratic Republic of the Congo, Ukraine, Bangladesh, Uzbekistan, Indonesia, Viet Nam, Japan, Italy, Ethiopia, the Philippines, Syrian Arab Republic, Romania, Mexico, Angola, Kazakhstan, Turkey, Thailand, Colombia, Ghana, Algeria and Spain *(5)*.

Greater access to more affordable, generic DAAs and strengthened government responses are driving the observed progress. However, the majority of people living with HCV worldwide are still not diagnosed and have no access to HCV treatment. Despite the possibility of procuring more affordable generic treatments, many countries have not yet seized this opportunity to initiate or scale up treatment services. Access to DAAs appears to be particularly poor among certain populations that are at very high risk for HCV infection, notably people who inject drugs. Globally, an estimated

c Note that these data are incomplete or lacking for some high-burden countries, including India, Nigeria and Thailand. Statements regarding data or trends for countries are based on information provided by national hepatitis programmes, health ministries and/or civil society organizations.

d Updated estimates for 2016, validated by countries, will be published in 2018.

8% of chronic HCV infections and 23% of new HCV infections are in people who currently inject drugs *(3)*, yet they have very limited access to HCV testing and treatment.

Although this report focuses on low- and middle-income countries, high DAA prices present major barriers in high-income countries as well and result in the "rationing" of treatment. Very few high-income countries are able to procure generic versions of DAAs currently. While some countries have negotiated price/volume agreements or price reductions and are expanding access to treatment, overall progress is still slow (Box 3).

If countries are to reach the goal of elimination, they will need to rapidly and efficiently introduce an array of improvements, including in infection prevention and control, screening and diagnosis, and treatment uptake.

BOX 3. RECENT DEVELOPMENTS IN HIGH-INCOME COUNTRIES

Australia has shown strong government commitment by building solid capacity to screen and diagnose large numbers of patients. Almost 40 000 of the estimated 230 000 people living with HCV have initiated HCV therapy since the new DAAs were placed on the Pharmaceutical Benefits Scheme (which reimburses patients' treatment expenses) in March 2016 *(6)*. This came after a five-year price deal was struck with an originator company, based on anticipated volume (treating an estimated 62 000 people for AUS$ 1 billion) *(7)*. Increased use of general practitioners and other non-specialist clinicians for prescribing these treatments is also making it easier to reach diverse populations. By December 2016, general practitioners were writing about one third of DAA prescriptions in the country *(6)*.

As in many other countries, high prices of DAAs in **Canada** have limited access to treatment *(8)*. A move to pool the DAA demand of the country's provinces has led to price reductions and could widen access to treatment. The most recent estimates show that between 220 000 and 246 000 people are chronically infected with HCV in Canada *(9)*.

In **France**, where an estimated 193 000 people live with chronic HCV, between 80 000 and 90 000 people had been treated with DAAs by the end of 2017. The national viral hepatitis elimination plan includes provisions for reimbursing the entire cost of HCV tests and DAA therapy under the national health insurance scheme. Specific efforts are made to reach people who inject drugs, persons in prisons, migrants and persons coinfected with HIV.

Spain provides HCV treatment free of charge to eligible patients who have mild-to-severe fibrosis, 72 000 of whom had received treatment by early 2017. Reinfections are also treated. The prices of DAAs, which are obtained from originator companies, range between US$ 8000 and US$ 14 000 for a 12-week treatment course.

In **Switzerland**, patients with mild fibrosis who had no complications were initially not eligible for reimbursement of HCV treatment. Some health insurers have allowed those patients to purchase generic DAAs through "buyers' clubs" at much lower prices than those available in Switzerland with the consent of the regulatory authority *(10)*. In mid-2017, the country expanded reimbursement to all patients after negotiating slightly reduced prices for new DAAs from originator companies *(11)*. It is estimated that between 50 000 and 80 000 people in Switzerland are living with HCV *(12)*.

In the **United Kingdom**, where an estimated 214 000 people were living with HCV in 2016, increased treatment with DAAs led to a drop of almost 10% in the annual number of HCV-related deaths between 2014 and 2016. The number of people accessing HCV treatment each year doubled during that period, from approximately 6000 to 12 000 *(13)*. The treatment, which is available through the National Health Service, remains expensive, however. The price of a combination of sofosbuvir and velpatasvir in 2016 ranged from approximately US$ 10 500 to US$ 17 000 for a 28-day supply *(14)*. Price negotiations with originator companies are confidential. The United Kingdom reportedly is seeking an agreement similar to the one reached by Australia.

In the **United States of America** (USA), an estimated 3.5 million people were living with HCV in 2015 *(15)*. The National Academies of Sciences, Engineering, and Medicine have proposed a national strategy for the elimination of hepatitis C, which highlights the high costs of DAAs and lack of access to affordable health care as major obstacles to large-scale and equitable treatment *(16)*. A recent study found that almost half of Medicaid patients were refused hepatitis C treatment, compared to about 10% of patients who had commercial insurance *(17)*.[e]

e Medicaid is a joint Federal–State programme that provides free or low-cost health coverage to low-income individuals and families.

2.2 SCREENING AND DIAGNOSIS COVERAGE REMAINS LOW

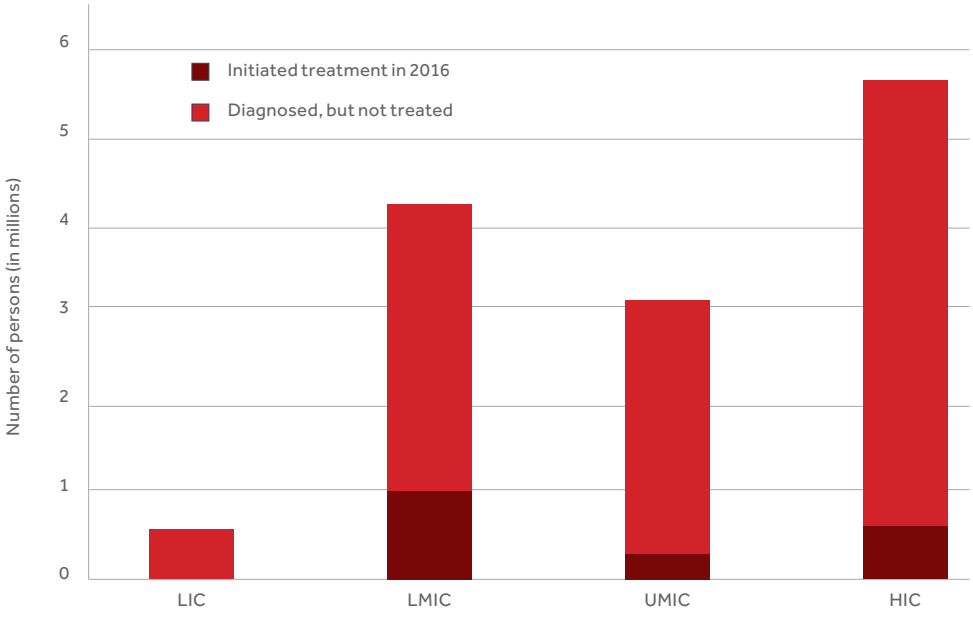
Globally, in 2016, about one in five people living with HCV had been diagnosed. In low-income countries, only about 8% of people infected with HCV had been diagnosed, compared with 43% in high-income countries (Fig. 2.1). Offering HCV screening and diagnosis to people who are at high risk of infection and could be reached relatively easily would expand treatment uptake. Those groups include people who inject drugs and who are already using harm reduction services, people with HIV who are on antiretroviral therapy, and prisoners or detainees.

As currently practised, the clinical management of HCV requires sophisticated laboratory capacity to diagnose infection, identify the genotype, assess fibrosis and determine appropriate treatment regimens for individuals *(18)*. It is important to simplify diagnostic tools and processes so that they provide results in a single visit and can be used across a range of settings, including in community health facilities *(19)*. WHO issued the first guidelines on testing for chronic HCV (and HBV) infection in February 2017 *(18, 20)*.

The prices of diagnostics are decreasing, though in most countries patients usually have to pay at least part of the costs themselves *(21)*. Rapid diagnostic tests for HCV antibodies currently cost as little as US$ 1, though assays using oral fluids are more expensive, at about US$ 8–10.[f] However, confirmatory tests can cost between US$ 15 and US$ 100, depending on the diagnostic product and country *(22)*. Affordable, one-step, point-of-care testing would make it possible to identify much larger numbers of people in need of treatment. Annex 1 presents pricing data for the most current diagnostics.

WHO has prequalified both rapid diagnostic tests for HCV antibodies *(23, 24)* and HCV RNA assays that allow for confirmation of chronic HCV infection even in remote areas *(25)*. A larger number of WHO-prequalified in vitro diagnostics would broaden countries' options, and ease the procurement and use of high-quality in vitro diagnostics for HCV.

Fig. 2.1. Number of people diagnosed with HCV who initiated treatment in 2016, by country income group



HIC: high-income countries; LIC: low-income countries; LMIC: lower-middle-income countries; UMIC: upper-middle-income countries

Source: WHO presentation to the World Hepatitis Summit, 1–3 November 2017, São Paulo, Brazil. Based on data from the Center for Disease Analysis/Polaris.

f By ordering a very large number of tests, Egypt has negotiated the price per test down to about US$ 4.

2.3 TREATMENT OPTIONS HAVE INCREASED

DAAs eliminate HCV from the body by preventing the virus from multiplying. In more than 95% of cases, they cure individuals of HCV, usually within 8–12 weeks *(26)*.[g] Since late 2013, five single-component DAAs and six fixed-dose combinations have received regulatory approval from at least one stringent regulatory authority.

Therapy continues to evolve. New regimens are showing improved efficacy, becoming simpler and easier to prescribe, and include options that are effective against all six major genotypes of HCV. Wider access to such pangenotypic DAA medicines would be a major boost, since such regimens remove the need to perform complex and expensive pretreatment genotype testing. They also simplify both the choice of treatment regimen and the procurement and distribution of HCV medicines. Such advances also improve the prospects for scaling up treatment in primary health care settings by using non-specialist providers – similar to the task-shifting and decentralizing breakthroughs that have transformed the HIV response *(27)*.

A pangenotypic fixed-dose combination of sofosbuvir and velpatasvir was approved by the United States (US) Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) in mid-2016, but it is not yet available in most low- and middle-income countries. As of mid-2017, the regimen was registered in only three low- and middle-income countries, and there were very few generic producers of the regimen. The approval in mid-2017 of the fixed-dose combination of glecaprevir and pibrentasvir, the most recent pangenotypic regimen, is expected to further improve therapeutic options for HCV treatment. Studies have shown that cure rates of over 98% can be achieved, while adverse events have been mild. Both the FDA and EMA have approved this new regimen *(28)*. However, as of December 2017, the originator company had neither announced any access programme for low- and middle-income countries nor had it licensed its hepatitis products to the Medicines Patent Pool. It remains to be seen at what price level the regimen will be marketed to low- and middle-income countries.

Further treatment combinations are in development. The Drugs for Neglected Diseases *initiative* (DND*i*) is conducting phase II/III trials in **Malaysia, South Africa** and **Thailand** to assess the efficacy and safety of a combination of sofosbuvir and ravidasvir across all six major HCV genotypes *(29, 30)*.

2.4 PAEDIATRIC TREATMENT STILL LAGS BEHIND

While more treatment options for adults are coming to the market, approved treatment regimens for infants and young children are still lacking.

Until early 2017, no DAA had been approved for use in children. This meant that, in principle, pegylated interferon and ribavirin remained the standard of care for hepatitis C infection among children – an unacceptable situation in light of the new, more effective treatments that are available for adults.[h] The situation improved in April 2017 when the FDA approved supplemental applications for sofosbuvir and a combination of sofosbuvir and ledipasvir to treat HCV in children aged 12–17 years *(31)*. However, no product has been approved yet for children younger than 12 years. This gap must be closed *(32)*.

Clinical trials of other DAA-only regimens for children are being conducted *(29)*. Study findings presented in May 2017 indicated that an investigational dose of sofosbuvir and ledipasvir (ledipasvir 45 mg/sofosbuvir 200 mg) cured 99% of 6–11-year-old children living with HCV without any serious adverse events *(33)*. It is not yet known whether or when this may lead to an approved regimen for children younger than 12 years or when a promising pangenotypic regimen will be available for children.

g For genotype 3, cure rates tend to be slightly lower, at around 90%.

h The treatment is associated with a range of common adverse effects, including fatigue, depression, irritability and nausea. It can also affect growth, and lead to weight loss and neutropenia. *See* EASL recommendations on treatment of hepatitis C, 2015. J Hepatol. 2015;63(1):199–236.

3

EXPANDING ACCESS TO HEPATITIS C TREATMENT: CHALLENGES AND OPPORTUNITIES

Temur Radiani is living proof of the progress being made in access to hepatitis C treatment. After a long fight, he was finally cured of hepatitis C in 2017

CREDIT: WHO GEORGIA

Increased competition among different DAAs, including through voluntary license agreements and among originator producers, has led to a downward trend in prices. The steepest price cuts have been in low- and middle-income countries where several generic producers compete. Generic versions of sofosbuvir, sofosbuvir/ledipasvir and daclatasvir are available from a range of manufacturers from countries such as **Argentina, Bangladesh**, **Egypt**, **India** and **Morocco** (*see* Section 3.2 and Appendix. Drug profiles). Generic manufacturers are also developing or already producing fixed-dose combinations that combine DAAs from different originators, such as sofosbuvir/daclatasvir.

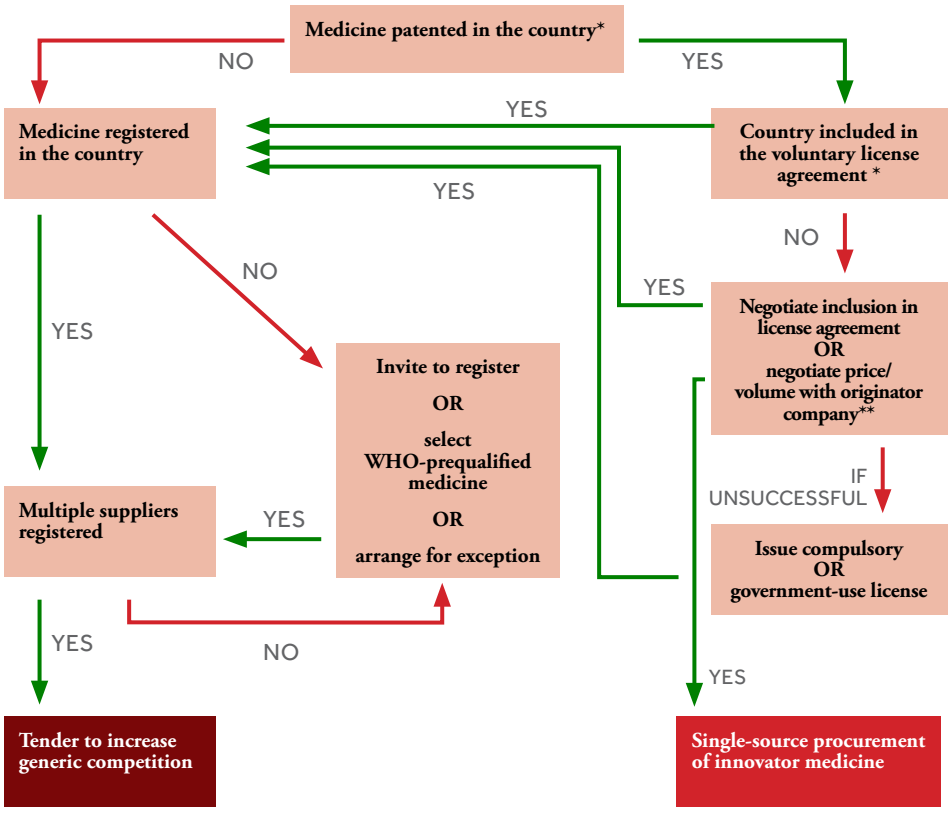
Prices of DAAs are also dropping among upper-middle- and high-income countries, though at a much slower pace and from high initial levels. They remain very expensive in many of those countries where patent protection blocks generic competition.

Box 4 describes a decision-making algorithm that countries can use to identify their main procurement barriers and select routes towards expanding access to DAAs.

BOX 4. HOW TO ACCESS HCV TREATMENT

As countries go about building their HCV treatment programmes, they encounter different sets of challenges. How countries negotiate these challenges depends primarily on the patent situation, whether the country is included in voluntary license agreements, and whether the DAAs are WHO prequalified or have been approved by a national regulatory authority (Fig. 3.1).

Fig. 3.1. Choosing a course of action to make direct-acting antivirals widely available



Note: This graphic is based on a chart developed by Medicines Law & Policy and is available, along with additional material such as a model government-use license, at: https://medicineslawandpolicy.org/tools/

* Check on www.medspal.org

** WTO TRIPS Agreement does not require previous negotiations for government-use licenses.

3.1 PATENT-RELATED BARRIERS REMAIN A CHALLENGE

All new DAAs are subject to patents that cover the chemical molecules or active ingredients, manufacturing processes, methods of treatment and formulations. However, the patent situation differs from country to country, depending on whether a company has filed for a patent and whether the national or regional patent office has granted the patent. As countries use different criteria and practices for granting patents, the same patent application may be granted in one country and rejected in another *(34,35)*. Comprehensive patent data on all DAAs and further explanations can be found in MedsPaL *(2)*, the patent database of the Medicines Patent Pool, and in WHO and UNITAID reports on the patent situation of various DAAs *(29)*.

Where compound patents are not filed or granted, it opens the way for local production or importation of generic products, as was the case in **Georgia** and **Morocco**, for example, where the primary patents for sofosbuvir were not filed. Generic companies located in countries where there are no patents (e.g. **Bangladesh**) or patents only on certain DAAs (e.g. **Egypt** and **Morocco**) can export their products to all other countries where the relevant patents have not been filed or granted.

Most national patent laws provide third parties with an opportunity to file observations or patent oppositions with the patent office. This can be done, for example, to register concerns about the fulfilment of patentability requirements, such as the assessment of the novelty and inventiveness of a patent application. By helping to ensure that patent applications are examined diligently and granting of unwarranted patents is prevented, patent oppositions can facilitate generic competition.

Some NGOs are systematically filing patent oppositions on certain patents covering sofosbuvir and other DAAs, arguing that these do not fulfil the necessary conditions of inventiveness and novelty. These interventions have led to the rejection of some key patent applications for sofosbuvir in **Brazil**, **China**, **Egypt** and **Ukraine** *(36)*. The European Patent Office has reduced the scope of one of the main patents on sofosbuvir after civil society organizations filed oppositions *(37)*.[i] NGOs have also filed patent oppositions in **Argentina**, **India**, the **Russian Federation** and **Thailand** *(38)*. Where successful, such interventions can facilitate generic competition.

Even where patents do not cover certain DAAs, data exclusivity can block access to generic products. Data exclusivity prevents the generic manufacturer and the national regulatory authority from relying on the clinical data submitted by the originator company to register a generic version of the same product for a certain period of time. While the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) requires the protection of such data against disclosure and unfair competition, it does not require data exclusivity.

In **Ukraine**, Gilead challenged the registration of a generic product based on data exclusivity and began to engage in an investor-to-state arbitration process against the government, demanding compensation for damages. The dispute was settled, with Ukraine deregistering the generic product, thereby effectively blocking competition, and agreeing to procure the originator product from Gilead at a reduced price *(24,39)*. In August 2017, Gilead extended its license agreements to include Ukraine, opening the market to generic imports from its Indian licensees.

Voluntary licenses

The originator companies Gilead and Bristol-Myers Squibb (BMS) have signed voluntary license agreements that enable other producers to manufacture and/or sell generic versions of sofosbuvir, ledipasvir, velpatasvir (Gilead) and daclatasvir (BMS) in countries listed in the agreements ("the territory" of the license)*(1)*. Consequently, all countries that are included in these agreements can procure generic DAAs from the licensees at generally more affordable prices (*see* Section 3.2).

Gilead licensed its products directly to 11 generic manufacturers in **India**, allowing generic versions of its DAAs to be sold in over 100 countries. However, the Gilead license agreement excludes a significant number of middle-income countries with high burdens of HCV. In August 2017, Gilead expanded the territory of its license to include **Belarus**, **Malaysia**, **Thailand** and **Ukraine**, bringing to 105 the total number of countries included in the agreement.[j]

i Patent on the sofosbuvir/prodrug, EP2203462. Following the opposition, the patent was maintained in an amended form with the chemical formula being excluded from the claims. The patent applicant appealed the decision. In: European Patent Office: European Patent Register [website] (https://register.epo.org/application?number=EP08732818, accessed 5 February 2018).

j *See* https://www.linkedin.com/feed/update/urn:li:activity:6306624759572631552/, accessed 6 February 2018.

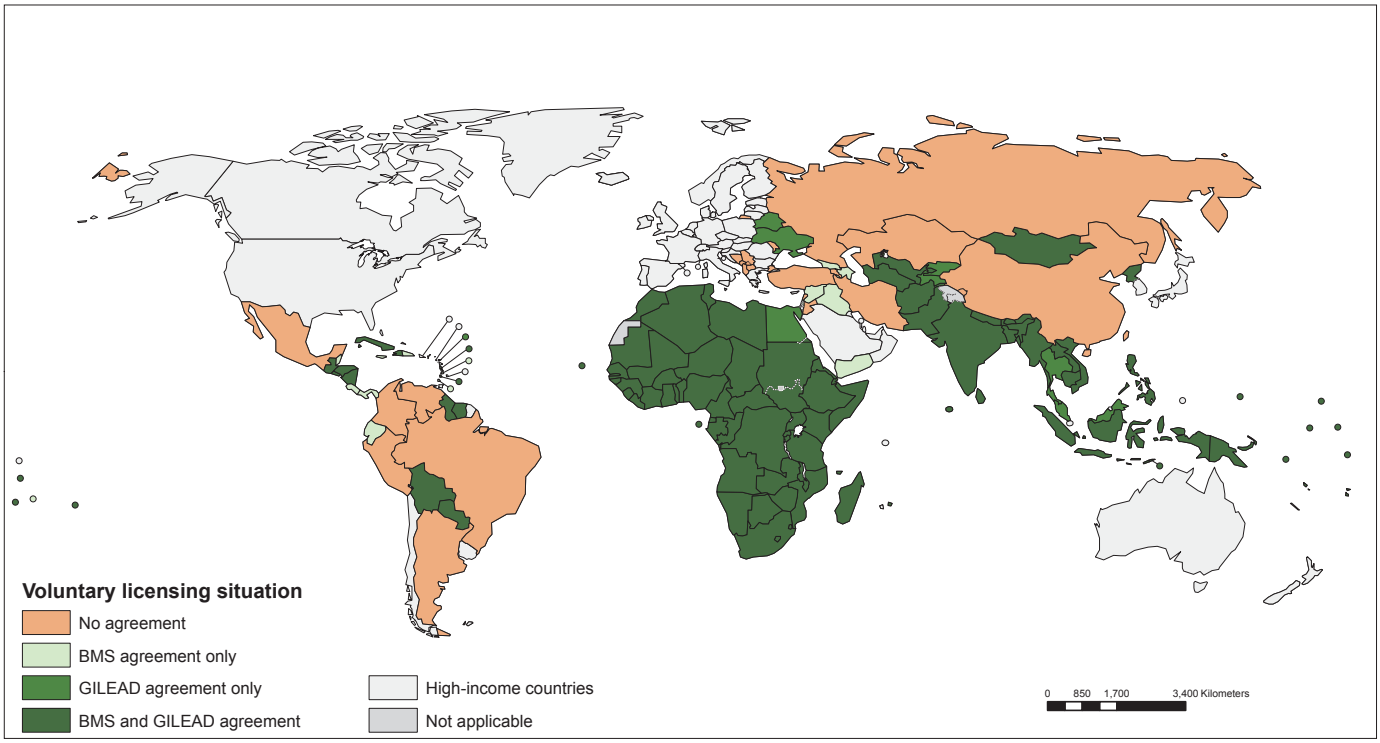
BMS signed a voluntary license for daclatasvir with the Medicines Patent Pool in November 2015. The agreement includes 112 countries (representing about 69% of the global HCV burden), including a majority of middle-income countries *(29,40)*. It also allows manufacturers to market generic versions of daclatasvir in countries where no patent has been granted as long as the manufacturing process does not rely on BMS technology. As of November 2017, a number of mostly upper-middle-income countries, including **Brazil**, **China**, **Colombia**, **Mexico**, **Kazakhstan** and **Turkey,** which together are home to an estimated 14 million people living with HCV, were not included in the license agreements (Fig. 3.2). Due to patent protection, they are not able to import or locally produce generic versions of the respective DAA medicines.

Price negotiations and compulsory licenses

Countries not included in voluntary license agreements have to use other strategies to reduce prices. **Australia**, for example, has successfully negotiated a price/volume agreement with originator companies. For countries in Latin America and the Caribbean, the Pan American Health Organization has engaged in pooled procurement (*see* Chapter 4).

Malaysia in September 2017 opted for another route and became the first country to issue a government-use license for a DAA. World Trade Organization members have the right to grant government-use or compulsory licenses. By doing so, they enable a local company to manufacture the specific patented product or to import it under certain conditions, as set out in their respective national patent laws *(1)*. By issuing such a license, Malaysia is now able to import or locally produce generic sofosbuvir while paying a royalty fee to the originator company *(41)*. Malaysia aims to obtain generic versions of sofosbuvir for as little as US$ 237 per 28-day course *(42)*, compared with the US$ 11 200 price reported earlier in 2017 for the originator version. After issuing the government-use license, Malaysia was included in the voluntary license agreement for sofosbuvir, ledipasvir and velpatasvir.

Fig. 3.2. Licensed territories for daclatasvir, ledipasvir, sofosbuvir and velpatasvir, low- and middle- income countries, 2017



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

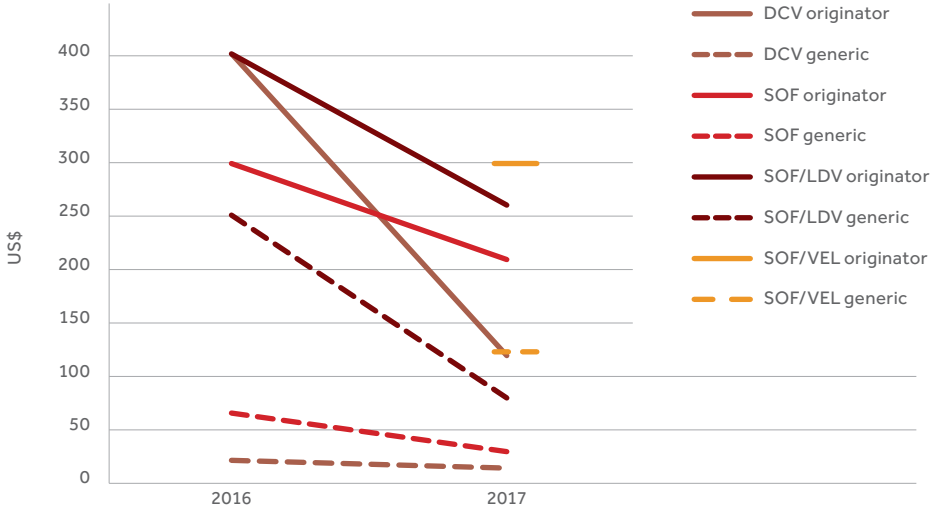
World Health Organization

3.2 PRICES ARE FALLING AS COMPETITION INTENSIFIES

The downward trend in prices continued in 2017 for both originator and generic DAA regimens, although wide disparities persist in the prices of originator and generic versions, including originator versions among countries in the same income groups (*see* Table 4.2 for greater detail).

Intensified competition, for example, in **Egypt** and **Mongolia**, has shifted market power in favour of purchasers, especially those with flexible procurement systems. Stronger competition among the originator products and increasing number of generic producers would maintain the downward pressure on prices (Fig. 3.3). However, sustaining a competitive environment also requires increasing the demand, so that quality production at lower prices remains viable, as achieved in the global scaling up of antiretroviral therapy for HIV.

Fig. 3.3. Trends in the lowest reported prices for direct-acting antivirals per 28-day supply, 2016–2017



Note: Prices as reported by DAA producers and countries in the WHO 2016 and 2017 surveys

Despite the positive developments in 2016–2017, countries where patents prevent generic competition generally still pay prices that put massive treatment scale up beyond the reach of national health budgets. Several countries with a high burden of HCV infection find themselves in that situation *(43)*. In those countries, DAA prices need to continue falling if treatment scale up is to accelerate.

Sofosbuvir

Sofosbuvir is currently the mainstay of HCV treatment regimens. Prices have fallen steeply, particularly for countries able to purchase generic versions (including all 105 countries listed in the voluntary license agreement, *see* Table 4.2).

Increased competition has resulted in a fall in prices as low as US$ 40 for a 28-day supply of sofosbuvir (as reported to WHO by companies) and US$ 20 (the price reported by **Pakistan** for locally produced sofosbuvir) in 2017. The originator company, Gilead, was offering a 28-day supply at US$ 212 to some countries in its licensed territory in 2017, down from US$ 300 in 2016.

Thus, the 105 countries that are included in the license agreement are able to proceed with competitive tendering that targets the lowest prices from generic companies with sublicences. Countries where there are no patents for sofosbuvir can access it at even lower prices, as demonstrated by the **Pakistan** example.

In 2017, WHO for the first time prequalified a generic active pharmaceutical ingredient (API) for hepatitis C treatment, in this case for sofosbuvir. By prequalifying the API, WHO has identified a quality source for generic manufacturers who wish to produce sofosbuvir. This move is expected to increase the availability of affordable generic medicines and help broaden treatment access.

In many upper-middle-income countries, sofosbuvir prices are still very high and they vary by wide margins. In mid-2017, a 28-day supply of sofosbuvir from the originator company was costing **Malaysia** US$ 11 200, nine times more than the procurement price of **Brazil**, for example (*see* Table 4.2).

Daclatasvir

Prices of daclatasvir have also decreased, though very unevenly. The lowest price reported by a country for the originator product in 2017 was in **Myanmar**, where a 28-day supply cost US$ 118. By far the lowest price reported for a generic version was in Egypt (where there is no patent for daclatasvir) – US$ 7.50 for a 28-day supply (*see* Appendix. Drug profiles). In other low- and middle-income countries, prices for the same supply of generic daclatasvir ranged from US$ 45 in **Mongolia** to US$ 150 in **Uzbekistan**.

These price levels are making it possible to procure a combination of sofosbuvir and daclatasvir at low prices. In October 2017, Médecins Sans Frontières announced that it had procured such a combination for US$ 120 for a 12-week course *(44)*.

The 112 countries that are included in the daclatasvir license agreement are able to use competitive tendering to secure the lowest possible prices from generic companies with sublicences (*see* the appendix on drug profiles). **South Africa**, an upper-middle-income country, procured generic daclatasvir for US$ 150 from sublicensees. Upper-middle-income countries not included in the license agreement are paying higher prices for a 28-day supply sourced from the originator company – for example, US$ 1300 in **China** and US$ 3740 in **Malaysia** in mid-2017. These countries can seek more affordable prices through price/volume agreements or by using TRIPS flexibilities, as **Malaysia** has done with regard to sofosbuvir.

Sofosbuvir/ledipasvir

A 28-day supply of sofosbuvir/ledipasvir, sourced from the originator company, Gilead, costs US$ 280 in **Rwanda** in 2017, but **Viet Nam** (like **Ukraine**, a lower-middle-income country) reported an originator price of US$ 680 in 2017. Prices reported in upper-middle-income countries for the originator product were as high as US$ 14 227 in **Malaysia**.

Generic versions of sofosbuvir/ledipasvir were being procured at much lower prices: US$ 200 or less in several low- and lower-middle-income countries, and approximately US$ 300 in **South Africa**, an upper-middle-income country. The lowest reported price from a generic company was US$ 75 for a 28-day supply (see Appendix. Drug profiles).

The 105 countries that are included in the license agreement, as well as other countries where there are no relevant patents, can proceed with competitive tendering to target the lowest prices from generic companies with sublicences (*see* the appendix on drug profiles). Countries not included in the agreements can try to lower prices through price/volume agreements or by using TRIPS flexibilities.

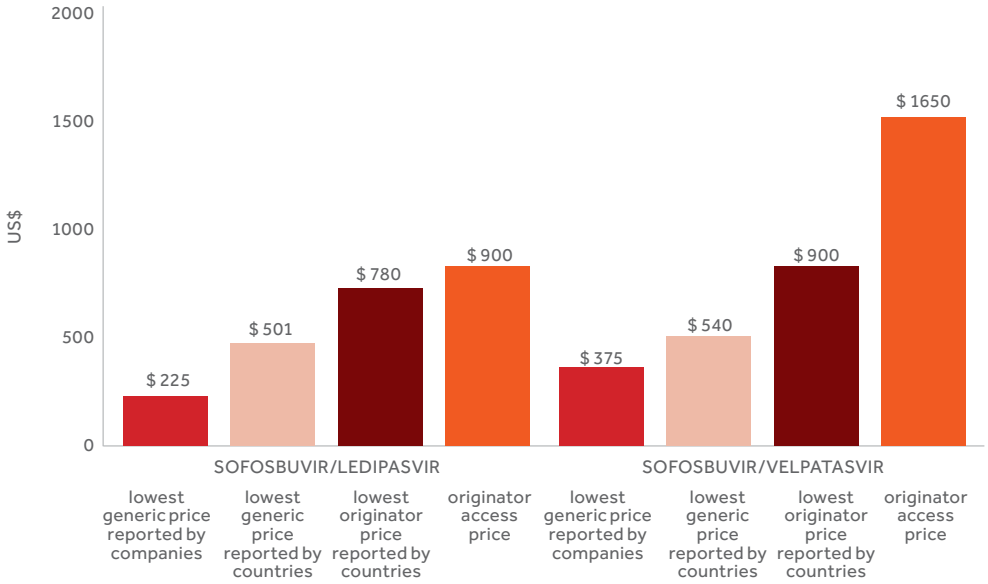
Sofosbuvir/velpatasvir

The pangenotypic regimen sofosbuvir/velpatasvir is unevenly available in low- and middle-income countries and at widely varying prices. The originator company, Gilead, does not offer flat pricing for this treatment regimen in the countries included in its licensed territory (unlike for sofosbuvir and sofosbuvir/ledipasvir).

South Africa reported that sofosbuvir/velpatasvir was available at US$ 550 per 28-day supply in 2017 from the originator, while the Pan American Health Organization's regional procurement initiative had initially negotiated a price of US$ 2600 for a supply of the same from Gilead and, more recently, at US$ 1600. Only **Pakistan** reported having a generic version available, at US$ 180 per 28-day supply. However, three generic companies reported prices that ranged from US$ 130 to US$ 350 for a 28-day supply. It is expected that the market competition for this pangenotypic regimen will be as dynamic as that for sofosbuvir, once generic production increases and the regimen is registered more widely.

Fig. 3.4 gives the prices of a three-month course of generic and originator versions of DAA regimens in 2017.

Fig. 3.4. Prices of 3-month course direct-acting antiviral regimens for hepatitis C, 2017



Greater market transparency would facilitate price cuts

Countries are trying to negotiate reduced prices with manufacturers, but to do so, they require market intelligence on what other countries and buyers are paying. Price transparency of DAA regimens, particularly for high-income countries, remains inadequate, and even the published prices are not always a reliable benchmark.

Some purchasers, such as **Canada** and **Ukraine**, have entered into confidential pricing agreements that may include significant rebates from manufacturers – arrangements that hide the actual prices being paid. Manufacturers use this method to bolster their positions when negotiating prices in other markets. Greater market transparency is needed if countries are to succeed in negotiating more affordable prices.

3.3 MORE PREQUALIFIED TREATMENT AND DIAGNOSTIC OPTIONS ARE NEEDED

While competition from generic manufacturers has driven down the prices of DAAs, most generic suppliers do not yet offer prequalified products or products approved by a stringent regulatory authority.

WHO's prequalification service assesses a wide range of medicinal products, thereby enabling countries and agencies to select medicines that meet acceptable quality standards. These products are listed in the WHO roster of prequalified medicinal products. A large number of WHO-prequalified DAAs and in vitro diagnostics would broaden procurement options.

As of February 2018, WHO had prequalified three generic sofosbuvir tablets, as well as the daclatasvir tablets of the originator company *(45, 46)*. It has also prequalified one of the APIs for sofosbuvir. The majority of generic DAAs, however, are neither WHO prequalified (largely because the producers have not applied for prequalification) nor authorized by any other stringent regulatory authority. On the diagnostics front, WHO has prequalified two rapid tests for HCV antibodies *(23, 24)* and one HCV RNA assay for confirmation of chronic HCV infection *(25)*.

WHO evaluates the products submitted for prequalification on the basis of information provided by the manufacturers. For the past four years, the average time from acceptance of a dossier for assessment to prequalification (i.e. full assessment) has been 6–7 months. However, depending on a manufacturer's experience and priorities, it may take 18

months or more for a manufacturer to meet the requirements for prequalification, including demonstration of bioequivalence and preparation of a complete dossier for filing. WHO prequalification occurs most rapidly (within 1–3 months) if another stringent regulatory authority has approved the product previously. In the case of two of the prequalified generic sofosbuvir tablets, prequalification took about 20 months (WHO plus manufacturer time).

Several additional manufacturers are expected to obtain WHO prequalification for their generic formulations in the near future.[k]

BOX 5. DIRECT-ACTING ANTIVIRALS ON THE WHO ESSENTIAL MEDICINES LIST

WHO's *Model list of essential medicines*[l] currently includes seven DAAs for treating HCV (Table 3.1). New and existing medicines for the treatment of hepatitis C are reviewed every two years to ensure that the most effective and suitable options are included on the List.

Table 3.1. DAAs on the WHO Model list of essential medicines

Direct-acting antiviral regimen	Dose form and strength
Sofosbuvir	tablet 400 mg
Simeprevir	capsule 150 mg
Daclatasvir	tablet 30 mg and 60 mg
Dasabuvir	tablet 250 mg
Ledipasvir + sofosbuvir	tablet 90 mg + 400 mg
Ombitasvir + paritaprevir + ritonavir	tablet 12.5 mg + 75 mg + 50 mg
Sofosbuvir + velpatasvir	tablet 400 mg + 100 mg

Source: WHO Model list of essential medicines, twentieth edition. Geneva: World Health Organization; March 2017, amended August 2017.

k Detailed information on WHO-prequalified products is available at https://extranet.who.int/prequal/content/prequalified-lists/medicines, accessed 5 February 2018.

l The list is available at: http://www.who.int/medicines/publications/essentialmedicines/en/, accessed 5 February 2018.

3.4 DAA MEDICINES SHOULD BE REGISTERED IN MORE COUNTRIES

Generally, the registration picture indicates the extent to which different DAAs are available in countries. Market authorization is required if a pharmaceutical product is to be procured and used in a country. To obtain such authorization, the manufacturer has to apply to the national regulatory authority for registration of the product in the country.

If a DAA is not registered in a country, it can significantly delay or impede the availability of the regimen. Although some countries have exceptional importation channels for unregistered drugs, these benefit a small minority of patients. If registrations increase, procurement choices broaden and countries can use those options to negotiate more favourable pricing and other arrangements for products to treat HCV.

There has been an increase in the number of countries where national regulatory authorities have approved generic and originator DAA regimens.[m] In 2017, at least one originator or generic version of sofosbuvir was registered in 56 low- and middle-income countries. For daclatasvir, at least one originator or generic version was registered in 23 low- and middle-income countries in 2017, but there were only eight countries where at least one generic version had been approved. Despite the promising trends, this still means that quality-assured sources of these DAAs (from the originator or a generic company) have been registered in a minority of low- and middle-income countries.

As of November 2017, the originator version of sofosbuvir had been registered in only 30 low- and middle-income countries, 17 of which were in the Gilead licensed territory. The originator version of daclatasvir was registered in 17 low- and middle-income countries, of which only one was part of the BMS voluntary license agreement.

Since the originator or generic manufacturers typically need to initiate the registration process, the current situation may reflect disinterest on the part of some companies to register DAAs in countries that are not seen as profitable markets. More collaboration among regulatory authorities would also make it easier for companies to register their products, in particular in small markets, and thus speed up registration.

The lack of country approvals for pangenotypic regimens is a major concern. Neither the originator nor the generic companies that market the pangenotypic regimen sofosbuvir/velpatasvir have filed a prequalification dossier with WHO. The originator version (Gilead) has been registered in the European Union, seven other high-income countries and only four low- and middle-income countries (**Argentina**, **Georgia**, **Lebanon** and **Mexico**). In mid-August 2017, the latest pangenotypic formulation, glecaprevir/pibrentasvir, was approved in the European Union and the **United States of America** *(29)*.

[m] Real-time data on registration is available at mapCrowd.org, a collaboration between Médecins du Monde and the Treatment Action Group.

4

OVERCOMING ACCESS BARRIERS: EXPERIENCES OF SELECTED COUNTRIES

Ya Yun and Xiao Jie from China were cured of hepatitis C thanks to DAA treatment

CREDIT: WHO CHINA

Country experiences show that a number of basic building blocks must be in place if access to treatment for HCV infection is to reach levels that bring the elimination targets within reach. WHO monitors and will continue to report on the main challenges and breakthroughs as countries develop and expand their treatment programmes. Tables 4.1 and 4.2 summarize the situation in the 23 countries that WHO surveyed for this report.[n]

Table 4.1. Summary of country responses for expanding access to HCV treatment, mid-2017

	National plan & treatment guidelines	Government response	Civil society activities	Access highlights & main challenges
AFRICAN REGION				
Cameroon (LMIC)	A national programme was created in 2015. National protocols were last updated in July 2017 to include DCV, in addition to SOF/LDV. A decentralized programme is being implemented to reach more patients. No information on treatment uptake was reported.	The government subsidizes the cost of drugs and laboratory testing, and waives certain taxes to reduce the cost of DAAs. The government is negotiating prices with pharmaceutical companies and makes use of voluntary licensing and absence of patents (1 generic version of SOF and 1 of SOF/LDV are available).	Participates in clinical trials. FIND is running a project in Cameroon to promote innovative diagnostic strategies for HCV. There are demonstration projects on DAAs in Yaoundé, with PharmaAccess and Joep Lange Institute.	The costs of HCV treatment and laboratory testing remain very high. Decentralization is continuing, along with capacity-building. Viral hepatitis surveillance is being implemented. Strategic guidance is being developed and validated, and advocacy is being strengthened.
Rwanda (LIC)	An HCV programme incorporating DAAs was established in October 2015. Treatment protocols were issued in September 2015. In 2015 and 2016, respectively, 300 and 1000 patients initiated treatment.	Negotiations are ongoing with Gilead and insurance schemes. The MoH is training additional staff. The MoH provides treatment in national, provincial and district hospitals.		There are financial barriers to access. Lack of WHO-prequalified generics has limited procurement options. No generics are available in the country, although the country is included in the license agreements.
South Africa (UMIC)	The MoH is preparing the National Viral Hepatitis Management Guidelines and a five-year action plan. In 2016, 160 patients received treatment.	DAAs are available through Groote Schuur Hospital in Cape Town (a referral hospital) as part of a clinical trial.	Civil society organizations are involved in a community-based feasibility project to provide DAAs, together with the UK Medical Research Council. Also under way is a programme (with Médecins Sans Frontières) to treat genotype 5 infection with SOF/DCV.	Financial barriers, lack of external funding and trained staff, absence of guidelines and protocols, and lack of registration (DAAs are imported through special authorization) are among the barriers. Registration is slow (SOF from Gilead was filed in December 2014). There is a need for access to a pangenotypic regimen. The epidemic affects mainly people who inject drugs. Criminalization of this key population and poor coverage of needle and syringe exchange block both prevention and treatment. South Africa is included in the relevant license agreements and thus could procure generic treatment.

[n] India, Nigeria and the Russian Federation did not respond to the survey.

Table 4.1. Summary of country responses for expanding access to HCV treatment, mid-2017 *(continued)*

	National plan & treatment guidelines	Government response	Civil society activities	Access highlights & main challenges
REGION OF THE AMERICAS				
Argentina (UMIC)	National programme created in 2012, and treatment protocols with DAAs since November 2015. In 2016, 1200 patients received treatment.	National programme expansion has slowed after initial treatment of 1200 patients. A strategic plan exists, but no specific budget has been allocated. Locally manufactured generics from two companies compete with originator products to supply the national programme.	There is pressure from civil society to increase access to DAAs.	Local production of SOF, but prices still high. Patent is pending and future options will depend on whether it is granted or not. The patent application was opposed by civil society. Registration progress was slow, but recent approval of SOF/VEL suggests this is changing.
Brazil (UMIC)	Treatment protocols were updated in August 2017 to expand treatment eligibility to fibrosis stage 2 (F2) regardless of time of diagnosis and to include the D/O/P/r regimen. Almost 7500 people were treated in 2015, rising to over 41 200 in 2016.	Brazil has a large programme that targets elimination. The revision in treatment eligibility criteria increases the number of patients eligible for treatment to 80 000.	Civil society is active in demanding universal access to treatment.	Brazil can import only originator products unless the country is included in the voluntary licenses or issues a compulsory license.
EASTERN MEDITERRANEAN REGION				
Egypt (LMIC)	National protocols were updated in December 2016 for patients with relapse and treatment failure. Current protocols include DCV, D/O/P/r, SMV, SOF, SOF/DCV and SOF/LDV. 30 000, 100 000 and 700 000 patients received treatment in 2014, 2015 and 2016, respectively.	There is a strong government response. National programme targets elimination. Support for local production, fast-track registration and nationwide treatment facilities contribute to accelerated access.	Local NGOs are involved in increasing access to DAAs. Patents were either not filed or rejected after patent oppositions were supported by civil society groups. Egypt is participating in a DND*i* clinical trial (SOF/RDV).	Egypt is a high-burden country. There are very high variations in prices between the public and private sector. Few patients undergo sustained virological response monitoring, which makes it difficult to follow up on cure rates.
Morocco (LMIC)	The national HCV programme was modified in March 2016 and treatment protocols were updated, In 2017, treatment reached about 10 000 patients. 100 and 6500 patients received treatment in 2015 and 2016, respectively.	The government supports local production and recently committed to elimination of HCV. At least 2 local manufacturers are operating.	Civil society is very active in demanding more affordable DAAs.	Only patients with health insurance receive DAAs. The registration process for DAAs and implementation of the national plan are slow.
Pakistan (LMIC)	Absence of national treatment programme, although the MoH issued protocols in September 2016. Provincial health departments manage their own treatment programmes. In 2015 and 2016, respectively, 65 000 and 161 000 patients received treatment.	Slow registration for some products. Most patients are treated in the private sector.	Médecins Sans Frontières manages a pilot programme using simplified treatment algorithms.	There is no national programme distributing DAAs. Strong generic competition exists (14 generic versions of SOF and 4 of DCV). In 2017, one generic company filed for SOF/VEL. A Gilead licensee distributes SOF/LDV locally.

	National plan & treatment guidelines	Government response	Civil society activities	Access highlights & main challenges
EUROPEAN REGION				
Georgia (LMIC)	A national HCV programme was established in 2015, targeting elimination by 2020. 5900 and 21 700 patients received treatment in 2015 and 2016, respectively.	The government negotiated an arrangement in 2015 in which Gilead agreed to donate DAAs for 10 years until elimination is achieved.	Civil society is working to ensure that more people who inject drugs benefit from treatment programmes. International NGOs (e.g. Médecins du Monde) support treatment operations in the country.	Georgia has significantly scaled up treatment. Co-payment policies vary by region, depending on local municipalities' contributions towards diagnostics. People who inject drugs need improved access to treatment.
Romania (UMIC)	A national HCV programme was created in April 2017. Criteria for treatment eligibility have been widened, increasing the number of eligible patients from 5000 to 12 000. In 2016, almost 6000 patients received treatment.	Treatment is provided in the public sector. The government initially contemplated compulsory licensing, reported that prices were negotiated with pharmaceutical companies based on volumes. However, prices remained confidential.	There is pressure for greater price transparency.	High prices in the absence of generic competition. Only 1 of 4 registered products is currently available to patients.
Ukraine (LMIC)	The HCV programme was established in 2015. National treatment protocols were last updated in July 2016. 2000 patients received treatment in 2015 and 2500 in 2016.	The government is negotiating with originators, and supports local and international NGOs that are operating treatment programmes.	Strong local NGOs are active in improving access to medicines. The Alliance for Public Health and Médecins Sans Frontières run treatment programmes and are strong advocates for universal access to treatment.	High prices of DAAs and an absence of registered generics are major challenges. Pharco filed for registration of SOF, but had to retract the application because of data exclusivity. According to information from Hetero, SOF was filed for registration in June 2015, but approval is still pending. Ukraine was included in the Gilead license territory in August 2017. DCV is not registered.
Uzbekistan (LMIC)	A national hepatitis programme was established in July 2017. No information on treatment was reported.	Generic versions of DAAs are available, but only in the private sector. There are plans to improve access to DAAs through the public sector.		Lack of access in the public sector, high prices of generic DAAs in the private sector with poor access in remote areas are major barriers. Medicine registration processes need to be accelerated and simplified. A pricing policy for essential medicines in the public sector would improve access.

Table 4.1. Summary of country responses for expanding access to HCV treatment, mid-2017 *(continued)*

	National plan & treatment guidelines	Government response	Civil society activities	Access highlights & main challenges
SOUTH-EAST ASIA REGION				
Indonesia (LMIC)	DAAs are included in the protocols of the updated national HCV programme. In 2016, 400 people were treated with a DAA-based regimen. There are plans to expand treatment to hospitals in 5 other provinces.	The MoH is at the initial phase of DAA deployment through national referral hospitals. Availability of DAAs in the public sector is uneven.	Support from the Clinton Health Access Initiative and a donation of DCV (from BMS) will enable treatment for 2000 HCV/HIV patients in 13 hospitals in DKI Jakarta and other provinces with large populations of people who inject drugs.	Health system constraints and limited choice of DAAs hinder access to treatment. Generic DAAs are not available.
Myanmar (LMIC)	Myanmar established its National Hepatitis Control Programme in 2017, and published a *National Strategic Plan on Viral Hepatitis (2016–2020)* and *Simplified treatment guidelines for hepatitis C infection*. In July 2017, the first public sector hepatitis C treatment programme was launched in 7 state-owned hospitals for 2000 patients, including HCV-monoinfected and HCV/HIV-coinfected patients.	The government has facilitated the introduction of several generics (4 versions of SOF, 2 of SOF/LDV and 1 of DCV).	Local civil society groups are pushing for greater access to DAAs. Médecins Sans Frontières runs a treatment programme. Local NGOs such as the Myanmar Liver Foundation and international NGOs are planning to include hepatitis C treatment as part of their programming work.	The Ministry of Health and Sports is the main funder of the HCV treatment programme. However, high prices of generic DAAs and diagnostics make it difficult to rapidly expand the programme.
Thailand (UMIC)	A national hepatitis programme exists, but an HCV treatment programme has not been implemented. Simplified treatment protocols are being developed. No information on treatment uptake was reported.	In August 2017, Thailand was included in Gilead territory, which is expected to reduce DAA prices and improve access in the country. Treatment access has been very limited, with prices high due to lack of generic competition for most DAAs. At the moment, there is a specific reimbursement stream in the National Health Security Office for HCV treatment using interferon and ribavirin.	Civil society was key to the inclusion of Thailand in the Gilead licensed territory. It is also active in filing a patent opposition for SOF. Coalition Plus is active in the country. Thailand participates in a DND*i* clinical trial for SOF/RDV. Civil society groups also manage buyers' clubs.	High prices of DAAs and lack of access to generics are major barriers. After its inclusion in the Gilead territory in 2017, Thailand announced the inclusion in its national Essential Medicines List of SOF and SOF/LDV (effective January 2018), along with plans for generic procurement and domestic production.

	National plan & treatment guidelines	Government response	Civil society activities	Access highlights & main challenges
WESTERN PACIFIC REGION				
China (UMIC)	The HCV programme is integrated with the HIV/STI programme. In 2015, the Hepatology Society of the Chinese Medical Association included the use of DAA-based regimens. Guidelines will be updated again in 2018.	The government has taken initial steps. Greater alignment of health-care provision and health insurance schemes would increase access.		Access is still low. Accelerated registration of DAAs would improve access to medicines. However, prices of registered DAAs remain high for patients who pay out of pocket.
Malaysia (UMIC)	A national programme was created in January 2017. However, financial commitment for scaling up screening and treatment has been lacking, as have national protocols. This is expected to change with the issuing of the compulsory license and inclusion in the Gilead licensed territory. No information on treatment was reported.	There are strong government efforts to reduce prices and achieve universal access. The government issued a government-use license for SOF. Malaysia participates in a DND*i* clinical trial for SOF/RDV.	Civil society has been very active.	Very high prices of DAAs. The inclusion in the Gilead territory and issuing of a government license for SOF in 2017 should lead to significant price reductions through generic competition.
Mongolia (LMIC)	The national hepatitis programme was modified in May 2017 to include the goal of eliminating HCV by 2020. National protocols were revised in April 2016. Treatment uptake increased from 100 in 2015 to 6500 in 2016.	Nationwide screening and fast-track registration exists.		People require health insurance to receive DAAs, although a government co-payment mechanism exists. Mongolia imports generics under the voluntary license agreement. There are 5 generic versions of SOF and SOF/LDV. Competition and absence of patents facilitated price reductions.
Philippines (LMIC)	A national viral hepatitis programme was established in 2016 but has not been implemented yet. No treatment protocols have been issued. No information on treatment uptake was reported.	The government has eased some regulatory requirements to speed up registration of DAAs. It also allows the use of unregistered DAAs through compassionate special permits.		Slow implementation of the national programme. Treatment will be provided by the MoH as soon as procurement is complete. Scale up initially focused on people who inject drugs and people living with HIV, and was later expanded more broadly. Treatment is currently available only in the private sector.
Viet Nam (LMIC)	No national hepatitis programme exists, although national guidelines for hepatitis C treatment (including for DAAs) have been approved by the MoH. There is no systematic mechanism for reporting treatment data.	The government signed a memorandum of understanding with innovator companies, allowing Viet Nam to access lower prices for their products. There are no strategic or scale-up targets.	Centre for Supporting Community and Development Initiatives and Médecins du Monde have been active.	Long drawn-out process for DAA registration. Only 1 DAA is registered so far, although more are imported under special authorization. This limits competition. DAAs are currently not covered by health insurance. However, the MoH is revising the health insurance reimbursement list to include DAAs. Only doctors at national, regional and selected provincial hospitals have the capacity to provide hepatitis C treatment.

Note: The data and other information presented in these tables are based on responses to the 23-country WHO survey and interviews, all conducted in mid-2017. While WHO has sought to confirm the accuracy of the data, descriptions of challenges and opportunities in countries reflect the analyses of survey respondents at the ministries of health.

DAA: direct-acting antiviral; DCV: daclatasvir; DND*i*: Drugs for Neglected Tropical Diseases *initiative*; D/O/P/r: dasabuvir + ombitasvir/paritaprevir/ritonavir; FIND: Foundation for Innovative New Diagnostics; HCV: hepatitis C virus; LDV: ledipasvir; LIC: low-income country; LMIC: lower-middle-income country; MoH: Ministry of Health; NGO: nongovernmental organization: RDV: ravidasvir; SMV: simeprevir; SOF: sofosbuvir; UMIC: upper-middle-income country; VEL: velpatasvir

Table 4.2. Summary of DAA procurement situation in countries, mid-2017

	Registered DAAs	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Voluntary license (VL)	Compulsory/ government-use license (CL)	Generic local production
AFRICAN REGION						
Cameroon (LMIC)	SOF Mylan	89.5		DCV, SOF, SOF/LDV, SOF/VEL	No	No
	SOF Genix, Gilead, Strides, Pharco					
	SOF/LDV Genix					
	SOF/LDV Gilead	401				
	SOF/LDV Mylan	143				
Rwanda (LIC)	DCV BMS	Donation (6000 bottles in 2016)		DCV, SOF, SOF/LDV, SOF/VEL	No	No
	SOF Gilead	240				
	SOF/LDV Gilead	260				
South Africa (UMIC)	DCV Natco	150		DCV, SOF, SOF/LDV, SOF/VEL	No	No
	SMV Janssn	750				
	SOF Gilead and Natco	250–400				
	SOF/DCV generic	550				
	SOF/LDV Gilead, Natco and Strides	300–600				
	SOF/VEL Gilead	550				
REGION OF THE AMERICAS						
Argentina (HIC)	D/O/P/r AbbVie			No	No	Yes
	DCV BMS	1869				
	O/P/r AbbVie					
	SOF ELEA, Ultra Pharma					
	SOF Gilead	2908				
	SOF Richmond	728				
	SOF/VEL Gilead					
Brazil (UMIC)	D/O/P/r AbbVie			No	No	No
	DCV BMS	686				
	SMV Janssen	686				
	SOF Gilead	1399				

	Registered DAAs	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Voluntary license (VL)	Compulsory/ government-use license (CL)	Generic local production
EASTERN MEDITERRANEAN REGION						
Egypt (LMIC)	DCV Pharco and 4 companies	7.50	12	SOF, SOF/LDV, SOF/VEL	No	Yes
	DCV BMS filed not yet approved	165	580			
	O/P/r AbbVie	380	520			
	SMV Janssen	165	560			
	SOF Gilead	275	315			
	SOF Pharco and 17 companies	50	52			
	SOF/LDV Gilead	440	820			
Morocco (LMIC)	DCV Galenica, Pharma 5		150	DCV, SOF, SOF/ LDV, SOF/VEL	No	Yes
	SOF Galenica, Pharma 5		300			
Pakistan (LMIC)	DCV Indian generic version		90	DCV, SOF, SOF/ LDV, SOF/VEL	No	Yes
	SOF 14 generic companies	20				
	SOF/LDV 14 generic companies		340			
	SOF/VEL 1 generic company		180			
EUROPEAN REGION						
Georgia (LMIC)	SOF Gilead	Donation		DCV	No	No
	SOF/LDV Gilead	Donation				
Romania (UMIC)	D/O/P/r AbbVie			No	No	No
	ELB/GRA MSD					
	SMV Janssen					
	SOF Gilead					
Ukraine (LMIC)	D/O/P/r AbbVie	2500		No	No	No
	SMV Janssen					
	SOF Gilead	250				
	SOF/LDV Gilead	300				
Uzbekistan (LMIC)	DCV Incepta (unclear if registered)	150		DCV, SOF, SOF/ LDV, SOF/VEL	No	No
	SOF Incepta	123				
	SOF/LDV Incepta	167				

Table 4.2. Summary of DAA procurement situation in countries, mid-2017 *(continued)*

	Registered DAAs	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Voluntary license (VL)	Compulsory/ government-use license (CL)	Generic local production
SOUTH-EAST ASIA REGION						
Indonesia (LMIC)	DCV BMS	Limited donation		DCV, SOF, SOF/LDV, SOF/VEL	No	No
	SOF Mylan	240				
	SMV Johnson & Johnson	400				
Myanmar (LMIC)	DCV Hetero	118		DCV, SOF, SOF/LDV, SOF/VEL	No	No
	SOF, Cipla, Genix, Mylan,	280				
	SOF/LDV Genix, Hetero	367				
Thailand (UMIC)	DCV BMS		1236	SOF, SOF/LDV, SOF/VEL (since August 2017, with estimated 28-day supply prices of US$ 140 for SOF and US$ 196 for SOF/LDV)	No	Yes
	O/P/r AbbVie					
	SOF Gilead		1236*			
	SOF/LDV Gilead		1648*			
WESTERN PACIFIC REGION						
China (UMIC)	DCV BMS	1300		No	No	No
Malaysia (UMIC)	D/O/P/r AbbVie	4050		SOF, SOF/LDV, SOF/VEL (As of August 2017, with prices expected to decrease)	Yes for SOF	No
	DCV BMS	3740				
	SOF Gilead	11 200*				
	SOF/LDV Gilead	14 227*				
Mongolia (LMIC)	DCV Mylan	45		DCV, SOF, SOF/LDV, SOF/VEL	No	No
	SOF Hetero, Natco, Strides	150				
	SOF Mylan, Patheon, Gilead	300				
	SOF/LDV Hetero, Mylan	250				
	SOF/LDV Natco	200				
	SOF/LDV Patheon, Gilead	300				
	SOF/LDV Strides	300				
The Philippines (LMIC)	SOF Gilead, Mylan			DCV, SOF, SOF/LDV, SOF/VEL	No	No
	SOF/LDV Mylan					
Viet Nam (LMIC)	SOF Gilead	250		DCV, SOF, SOF/LDV, SOF/VEL	No	No
	SOF/LDV Gilead	680				

* SOF prices of US$ 11 200 and US$ 1236, and SOF/LDV prices of US$ 14 227 and US$ 1648 were reported in Malaysia and Thailand, respectively, in the private sector. These countries were recently included in the licensed territory. The prices are expected to decrease in the near future.

BMS: Bristol-Myers Squibb; DAA: direct-acting antiviral; DCV: daclatasvir; D/O/P/r: daclatasvir + ombitasvir/paritaprevir/ritonavir; HCV: hepatitis C virus; LDV: ledipasvir; LIC: low-income country; LMIC: lower-middle-income country; O/P/r: ombitasvir/paritaprevir/ritonavir; SOF: sofosbuvir; UMIC: upper-middle-income country; VEL: velpatasvir

4.1 STRONG GOVERNMENT RESPONSES ARE NEEDED

Firm government resolve to achieve universal access to HCV treatment is a core foundation for the many other steps that are needed to eliminate HCV as a public health threat. Strong government commitment makes it possible to develop coherent treatment plans, allocate appropriate resources and pursue strategies that can expand access to treatment.

In **Egypt**, for example, government commitment laid the basis for widespread testing campaigns and the rapid scale up of the world's largest HCV treatment programme. Despite patent protection and exclusion from voluntary license agreements, the Government of **Brazil** established a programme that has provided treatment to almost 60 000 patients since 2015. Its new HCV treatment guidelines explicitly focus on reaching universal access to treatment – a big challenge, given the current high prices of DAAs available in the country.

Mongolia is another example of how strong commitment can be transformed into a systematic strategy. Starting with an epidemiological assessment, Mongolia modelled the future impact of interventions, developed costing scenarios, and estimated the budgetary impact of treatment scale up. A financial dialogue with stakeholders was then used to decide on funding mechanisms and devise ways to minimize out-of-pocket costs *(3)*. As a member of both BMS and Gilead's licensed territories, it then brought economies of scale into play, which helped drive down the price of generic daclatasvir as low as US$ 45 per 28-day supply. By late 2016, the government had incorporated HCV treatment in its national health insurance system, which covers 98% of the population. Individuals undergoing treatment are reimbursed with about US$ 265, irrespective of whether they use public or private health providers *(3)*. From end-2015 to mid-2017, Mongolia treated about 5300 patients with HCV infection in the public sector with a cure rate of well over 90%.

At the same time, several countries with substantial HCV epidemics still do not have national treatment plans or programmes. This is the case in much of eastern Europe and central Asia. **China** has taken initial steps but treatment access remains very limited. In **Argentina** and **Morocco,** and some other countries there are national treatment programmes but they lack sufficient funding, which restricts expansion of access to treatment. In addition, national treatment guidelines often do not exist or need to be revised and updated, which suggests that DAA-based HCV treatment is not yet being treated as a priority.

4.2 MARKET COMPETITION WILL LEAD TO REDUCED PRICES

Depending on a country's patent situation and whether it is included in any of the licensed territories, a range of options exist for purchasing DAAs. Countries where patents for the respective DAAs have not been filed or granted can legally manufacture or purchase any DAA. Countries included in the licensed territories for sofosbuvir, ledipasvir, velpatasvir and daclatasvir can purchase generics from licence holders and from other manufacturers if there are no patents (*see* Annex 2 for further details).

In **Egypt**, key patents for sofosbuvir were either not filed or were rejected, which led to vibrant competition between generic manufacturers, many of them local. In 2017, 18 generic versions of sofosbuvir and four of daclatasvir were available in Egypt, some at exceptionally low prices (*see* Chapter 3 and the appendix on drug profiles).

A more dynamic market is needed for sofosbuvir/velpatasvir. In 2017, five generic companies were reportedly manufacturing this pangenotypic regimen, but it has been registered in very few countries. This means that both competition and access to this important regimen remains extremely limited.

Increased competition from generic manufacturers around a wider range of DAAs will help drive down prices in countries that are not yet benefiting from the price reductions of the past two years.

4.3 INCREASED FINANCING OPTIONS SHOULD BE SOUGHT

While price reductions are making DAAs more affordable, there is still limited funding available in countries to purchase the medicines. Domestic financing remains low in most countries, while the lack of international and bilateral donor funding for HCV programmes was a recurring concern among government representatives, civil society organizations and public health experts consulted for this report. Some low-income countries may be able to attract increased external funding support but, for most countries, the treatment challenge demands increased domestic allocation for HCV programmes as part their move towards universal health coverage.

There are some encouraging signs from the Global Fund, which has indicated that it would consider including HCV components in country grant proposals in the context of HIV/HCV coinfection. As of October 2017, the procurement of daclatasvir and sofosbuvir was eligible for Global Fund support only in the context of treating HIV/HCV coinfection *(46)*.

Other entities are also providing valuable support. The Clinton Health Access Initiatve (CHAI)'s Quick-Start programme, which aims to cure 25 000 people of HCV in the next two years, is supporting ministries of health in **Ethiopia**, **Indonesia**, **Myanmar**, **Nigeria**, **Rwanda** and **Viet Nam**. CHAI has negotiated reduced prices with generic companies and one diagnostic manufacturer for use in this programme. Médecins Sans Frontières has HCV treatment projects in 11 countries, including in **Cambodia**, where funding from UNITAID and other sources supports its provision of free treatment for people living with HCV in Phnom Penh.

4.4 QUALITY ASSURANCE AND REGISTRATION OF MEDICINES AND DIAGNOSTICS ARE NEEDED

An efficient regulatory environment is a basic building block for successfully scaling up HCV treatment. Even when more affordable generic options are available to countries, they usually cannot procure them until national regulatory approval has been granted, hence the importance of in-country registration of DAAs, as discussed in Chapter 3. **Egypt** fast-tracked the registration of DAAs, which helped clear a path for rapid expansion of treatment access. **Mongolia** took a similar approach; after developing its national treatment plan in December 2015, it also fast-tracked its drug registration process, thereby allowing for the rapid introduction of generic DAAs (including five generic versions of sofosbuvir and sofosbuvir/ledipasvir, and one of daclatasvir).

Globally, however, the core DAAs have been registered in only a minority of countries; people in over 60 countries lack access to registered sofosbuvir, for example. For that to change, originator and generic companies and national regulatory authorities will need to prioritize the registration of DAA regimens. National regulators should also consider temporarily waiving some registration requirements (such as local phase III clinical trials) to facilitate quicker access to effective HCV treatment. Prequalification by WHO can support accelerated access in countries where DAAs have not been registered if governments waive registration for WHO-prequalified products.

The WHO Collaborative Registration Procedure, developed in 2012, also facilitates the registration of prequalified medicines and diagnostics in low- and middle-income countries. The support is aimed at helping countries clear their backlogs of pending applications for registration and strengthen their capacity to process the registration of medicines. The support applies only to WHO-prequalified products, however *(47)*.

4.5 THE USE OF EXISTING PROCUREMENT SYSTEMS COULD BE IMPROVED

Countries can use procurement processes much more effectively to scale up their HCV treatment programmes in a systematic manner. This involves a few steps. Clearly specifying the recommended treatment regimens in national treatment guidelines and ensuring that those medicines are registered are important for an effective procurement strategy. Up-to-date information about the patent status of regimens is vital for making these decisions. WHO has published patent reports on the various DAAs and updates them regularly *(48)*; a country-by-country summary of patent information on DAAs is also available at www.medspal.org.

Accurate estimates of the number of people living with HCV and eligible for treatment are another key element, along with setting treatment targets. These enable countries to take advantage of economies

of scale when negotiating prices with suppliers. By tying purchase orders to an ambitious treatment target, countries such as **Australia** and **Brazil** have successfully negotiated price reductions from originator companies.

Countries can strengthen their negotiating position further by procuring the regimens through tenders that invite manufacturers to bid or purchase through a pooled procurement mechanism. For example, the Pan American Health Organization through its Strategic Fund has been negotiating regionwide prices for DAAs with originator companies in this manner. Though a marked improvement on previously available commercial pricing, the prices available to countries where intellectual property agreements prevent access to generic DAAs remain substantially higher than current prices of generic products: sofosbuvir at US$ 1800 per 28-day supply; daclatasvir at US$ 1413. In early 2018, sofosbuvir/velpatasvir was renegotiated at US$ 1600 per 28-day supply and further volume-based price reductions are expected.

4.6 CIVIL SOCIETY INVOLVEMENT CONTRIBUTES TO EXPANDING ACCESS AND TREATMENT PROGRAMMES

Pressure mounted by civil society organizations is an increasingly important element in countries' bids to expand access to HCV treatment. Civil society groups campaigned strongly for the recent inclusion of **Malaysia** and **Thailand** in the Gilead licensed territory. Elsewhere they are important advocates for reduced DAA prices and for the removal of other barriers that restrict access to HCV treatment, especially for key populations such as people who inject drugs. Their sustained advocacy and ability to collaborate locally and network internationally underpin the roll-out of HCV treatment in many countries.

In several countries, local or international civil society organizations manage HCV treatment programmes for vulnerable populations who struggle to access treatment through government services. For example, in **Ukraine**, the Alliance for Public Health manages the treatment of vulnerable populations, who may sometimes miss out on services run by the Ministry of Health. Médecins Sans Frontières and Médecins du Monde operate treatment programmes in several countries, including **Cambodia**, **Myanmar**, **Pakistan**, **Ukraine** and **Viet Nam** *(24)*. In **Georgia**, Médecins du Monde has developed a pilot HCV treatment programme that is adapted for the specific needs of people who inject drugs *(49)*. Well-organized networks of local civil society groups are facilitating this work.

BOX 6. BUYERS' CLUBS ARE FILLING SOME GAPS

In the absence of health insurance schemes and other funding that cover HCV treatment, or where treatment is limited to patients with advanced liver disease, individuals have been importing DAA medicines themselves via the Internet, often by using the services of "buyers' clubs".

These methods of importation are not encouraged in many countries, though some (including **Australia**, **Italy**, **Switzerland** and the **United Kingdom**) do allow individuals to import a treatment course for personal use. In the case of Switzerland, individuals are allowed to buy up to three months' supply of hepatitis C medicines for personal use *(50)*.

Hundreds of buyers' clubs are active around the world, advising on facilitating the purchase of DAAs by individuals. Well-known clubs include Fixhepc.com (which offers individual consultations with doctors who recommend the appropriate treatment), Hepatitis C Treatment Without Borders, and the ITPC Buyers Club *(29)*. The medicines originate mostly from Indian generic manufacturers.

An Australian study conducted among patients treated with generics purchased individually or through a buyers' club (www.fixhepc.com in this case) showed similar clinical outcomes to those among patients using branded medicines. The study did not examine quality issues besides the purity of the API. Other factors that could influence quality include poor packaging (which can cause the product to degrade before the indicated expiry date) or cross-contamination with other products during manufacturing (which can increase toxicity).

Buyers' clubs are bringing DAAs within the reach of many individuals who otherwise would lack access to HCV treatment. But it remains essentially a stopgap response to the failure of public health systems to ensure equitable access to HCV treatment. There are also concerns that this method of purchasing DAAs may risk compromising other important aspects of treatment, including knowledge of a patient's medical history, treatment surveillance and management of interactions with other concomitant treatments.

5

CONCLUSION

People waiting for their appointments at the MSF Hepatitis C clinic in Cambodia

CREDIT: TODD BROWN

The existence of highly effective treatment for HCV and the steep reductions in the prices of these DAAs have transformed the outlook for this global epidemic. In 2016, the 1.5 million people who started DAA-based treatment accounted for a 50% increase in those accessing treatment compared with 2015.

However, a small number of countries have been responsible for much of the increase in treatment access. Leading the way is **Egypt**, which appears to be on track for eliminating its HCV epidemic by 2030, despite having had one of the largest epidemics in the world *(51)*. Other countries with substantial epidemics – including **Australia**, **Brazil, France** and **Georgia** – are also closing in on the elimination target. Their achievements need to be replicated on a much larger scale: despite the progress made since 2015, the vast majority of people living with HCV have not been diagnosed and have thus not initiated treatment.

The WHO survey findings show that strong generic competition leads to more affordable DAA prices, as experienced with HIV medicines. More than 100 low- and lower-middle-income countries, including some with a high burden of HCV infection, can now procure generic DAA regimens. The lowest reported price for a 28-day supply of generic sofosbuvir + daclatasvir has decreased to between US$ 30 and US$ 40. The lowest reported prices for a 28-day supply of pangenotypic sofosbuvir/velpatasvir was US$ 130 for a generic version and US$ 450 for the originator version. At the same time, many upper-middle-income countries and some lower-middle-income countries are still not included in one or both of the licensed territories and therefore have to procure DAAs at very high prices, which blocks expansion in access to treatment. The same holds true for nearly all high-income countries, where the absence of generic competition also limits the scope for price reduction.

Price reductions can be pursued along several routes. In addition to facilitating stronger competition between DAA producers, countries can use economies of scale or enter into pooled procurement and bulk purchasing arrangements to achieve reduced prices. Greater price transparency is needed if countries are to successfully negotiate price reductions. Countries can also use the TRIPS flexibilities available to them, as **Malaysia** has done by issuing a government-use license that will allow it to import generic versions of sofosbuvir at much lower prices than those offered previously by the originator company.

Countries that have achieved significant price reductions or that can procure DAAs at affordable prices now have to seize the opportunity and scale up treatment more rapidly as low prices alone do not guarantee access. This requires dealing with other challenges, including expanding screening and diagnostic services, and strengthening procurement and distribution systems for HCV medicines, promoting service delivery models that can reach those populations most affected, and integrating HCV testing and treatment into national health benefit packages to be delivered by public health services.

The regulatory and logistical environments also need to support expanded treatment access. Both originator and generic companies need to submit their DAA products to the WHO Prequalification Programme and register them in many more countries than is currently the case. A larger number of WHO-prequalified DAAs would broaden treatment options and ease the procurement and use of safe, effective and affordable regimens.

Furthermore, engaging in access programmes for low- and middle-income countries, especially for scaling up new pangenotypic regimens, should be a priority for innovator companies. User-friendly paediatric formulations also need to be developed.

Strong government commitment is a prerequisite for HCV treatment plans, financing decisions and institutional arrangements that are needed to roll out and sustain expanding HCV treatment programmes. Countries such as **Brazil, Egypt** and **Mongolia** are showing that robust government responses can be built in diverse settings.

To achieve HCV treatment targets, financing for HCV programmes must increase and, in most countries, will have to come from domestic sources, as part of a broader push towards universal health coverage. Countries can develop investment cases to demonstrate the potential long-term savings of a successful treatment programme and can advocate for increased public financing for HCV treatment. Price reduction strategies and enhanced programme efficiencies can help reduce the budgetary impact of treatment programmes.

The countries responsible for much of the expansion in treatment access over the past three years are showing that transformative HCV treatment programmes can be achieved rapidly and in different conditions. Other countries can now learn from and emulate these achievements. The momentum built and bold actions taken by several countries are encouraging examples of what can be achieved in a short space of time. However, unless many other countries, specifically those with a high burden of HCV infection, follow suit and purposefully scale up their programmes, the 2030 elimination target will slip out of reach. WHO will continue to support all countries as they set out along the path towards universal access to HCV treatment and the eventual elimination of HCV as a public health threat.

APPENDIX. DRUG PROFILES

1. DACLATASVIR

General information

- Therapeutic class: NS5A inhibitor
- Originator company: Bristol-Myers Squibb (BMS). The brand name of daclatasvir is Daklinza® *(52)*.
- First approved by the US Food and Drug Administration on 24 July 2015
- Daclatasvir is part of the preferred regimen for infection with genotypes 1, 3 and 4 in the WHO 2016 *Guidelines for the screening, care and treatment of persons with chronic HCV infection (53)*. It is included in the twentieth edition of the WHO *Model list of essential medicines*, published in March 2017 (amended in August 2017), and in the 4th Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team (April 2017) *(54,55)*.
- Optimus Pharma (India), Hetero (India), Cipla (India), Mesochem (China) and Laurus (India) manufacture the API and market it to finished product manufacturers.

Access, pricing and generic availability information

Access programmes in low- and middle-income countries

BMS has signed a voluntary license agreement with the Medicines Patent Pool, which enables the generic manufacture and sale of daclatasvir in 112 low- and middle-income countries. It also allows manufacturers to market generic versions of daclatasvir in countries where there are no patents, as long as they do not rely on BMS technology. Ten generic companies have signed the sublicensing agreements (Aurobindo, Beximco, Cipla, Emcure, Hetero, Laurus, Mylan, Natco, Sandoz and Zydus Cadila). BMS has tiered pricing in place *(40,56)*.

Generic production

Compared with 2016, four additional companies (**in bold**) now market daclatasvir: **Beacon**, Beximco, **Galenica**, Hetero, Incepta, **Mylan**, **Pharco**, Natco (did not respond to the 2017 questionnaire) and Pharma 5. Other companies are developing daclatasvir: Cipla is at the stability studies stage, while Aurobindo has daclatasvir under development.

Prices in low- and middle-income countries reported by innovator and generic companies and additional information on prices reported by countries

BMS did not report a price but stated that the "BMS tiered pricing model for daclatasvir takes into consideration several factors, including countries' economic development and burden of disease, as well as the response of the government to holistically address hepatitis C, including treatment and care." Prices for a 28-day supply of daclatasvir from BMS reported by countries in 2017 ranged from US$ 686 in Brazil to US$ 1869 in Argentina in the absence of generic competition (the two countries are outside the licensed territory), and as low as US$ 168 in Myanmar, where there is generic competition. There are no conditions stated by the originator to obtain discounted prices. Prices of generic daclatasvir range from US$ 7.50 in Egypt to US$ 143 in Morocco for a 28-day supply (*see* Table A1.1).

Table A1.1. Prices of daclatasvir 60 mg, per 28-day supply, as reported by companies and countries

Manufacturers	Marketing companies/ distributors	Country of origin	Local market prices		Export prices	
			Public (US$)	Private (US$)	Public (US$)	Private (US$)
BMS	BMS	United States of America	N/A	N/A	Licensed territory: 118 Not licensed territory: 165–1869	Licensed territory: 1236–3740
Beximco Pharmaceuticals Ltd.	Beximco Pharmaceuticals Ltd.	Bangladesh	92	92		
Incepta Pharmaceuticals Ltd.	Incepta Pharmaceuticals Ltd.		140	140	140	N/A
Galenica Pharmaceutical Laboratories	Galenica Pharmaceutical Laboratories	Morocco	172	N/A	N/A	N/A
Pharma 5	Pharma 5		143[a]	N/A	N/A	N/A
Pharco	Pharco[b]	Egypt	7.5	N/A	N/A	N/A
Mylan Ltd	Mylan Ltd	India	N/A	N/A	20[c]	N/A
Natco Pharma Ltd[d]	Natco Pharma Ltd[d]		61–70	N/A	70	N/A
	Abbott India Ltd		61	N/A	N/A	N/A
Hetero Labs	Hetero Labs		N/A	N/A	N/A	N/A
Zydus Cadila	Zydus Cadila		N/A	N/A	N/A	N/A

a Approximate price due to fluctuating exchange rate. Price applies only to the local market in Morocco.

b Four additional companies distribute daclatasvir at the same price.

c Indicative price reported by Mylan.

d Natco did not reply to the survey in 2017; prices are those reported for the 2016 edition. There is no indication that they have halted production/distribution.

Regulatory approvals and filings, and WHO-prequalified approvals and submissions

There have been no new approvals in the licensed territory (*see* Table A1.2). The sublicensees can sell outside the territory in countries where no patents are in force. BMS files and registers in markets where it intends to sell its products. The lack of registration of the originator may be problematic in some countries, although BMS appears willing to share data and facilitate generic registration *(40)* (*see* Table A1.2).

Table A1.2. Regulatory approvals and filings of daclatasvir by originator company in 2016 and 2017

2016				2017			
Approved LICs, LMICs, UMICs	Filed LICs, LMICs, UMICs	Approved territory	Filed territory	Approved LICs, LMICs, UMICs	Filed LICs, LMICs, UMICs	Approved territory	Filed territory
10	0	1*	0	17**	0	1*	0

* Rwanda

** Argentina, Brazil, Bulgaria, China, Colombia, Croatia, Egypt, Jordan, Lebanon, Malaysia, Mexico, Peru, Romania, Russian Federation, Rwanda, Thailand and Turkey.

LIC: low-income country; LMIC: lower-middle-income country; UMIC: upper-middle-income country

The number of generic daclatasvir filings and approvals has increased since 2016 (*see* Table A1.3). However, only in eight low-, lower-middle- and upper-middle-income countries is at least one generic version of daclatasvir approved (Cambodia, Chad, Gabon, India, Kyrgyzstan, Myanmar, Turkmenistan and Uzbekistan). If countries where the BMS product has received regulatory approval are included, the total number of countries with at least one version of approved daclatasvir rises to 25, including three countries (Brazil, China and Egypt) that rank among the ten countries with the highest burdens of HCV globally.

Table A1.3. Regulatory approvals and filings of daclatasvir by generic companies in 2016 and 2017

	2016		2017	
	Approved	Filed	Approved	Filed
Hetero	2	0	8	41
Incepta	0	0	2	2
Zydus	0	0	0	0

Daclatasvir by BMS was the first DAA to achieve WHO prequalification in October 2016. However, there are no prequalified generic versions of daclatasvir, which means that it is not possible to procure a generic WHO-prequalified pangenotypic daclastasvir/sofosbuvir regimen. None of the eight generic companies that responded to the 2017 questionnaire have filed for WHO prequalification, although Beacon, Cipla, Hetero and Mylan stated that they intend to file at the end of 2018, while Pharma 5 intends to file in 2018 and Beximco in 2019.

Patents

For an overall patent situation, please refer to the Medicines Patent Pool database, MedsPaL (http://www.medspal.org).

2. GLECAPREVIR/PIBRENTASVIR

- Therapeutic class: NS3/4A protease inhibitor + NS5A inhibitor
- Originator manufacturer: AbbVie. Brand name: Mavyret® (USA) *(57)*, Maviret® (EU)
- First approved by the US Food and Drug Administration on 3 August 2017
- Indication: fixed-dose combination of glecaprevir, an NS3/4A protease inhibitor, and pibrentasvir, an NS5A inhibitor, indicated for the treatment of all six major genotypes (GT1–6) of chronic hepatitis C
- Not included in WHO 2016 *Guidelines for the screening, care and treatment of persons with chronic HCV infection (53)* or the twentieth edition of the WHO *Model list of essential medicines* published in March 2017 (amended in August 2017) *(54)*, and not published in the 4th invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team (April 2017) *(55)*.
- Glecaprevir was developed by Enanta Pharmaceuticals. It was designed to enable once-daily dosing. AbbVie developed pibrentasvir.
- AbbVie has not announced an access programme, or any tiered pricing scheme or plans for a voluntary license.
- Beacon and Mylan have stated an interest in developing a generic version.
- For an overall patent situation, please refer to the Medicines Patent Pool database, MedsPaL (http://www.medspal.org).

3. OMBITASVIR/PARITAPREVIR/RITONAVIR ± DASABUVIR[o]

- Therapeutic class: NS5A polymerase inhibitor + protease inhibitor + non-nucleoside NS5B polymerase inhibitor
- Originator company: AbbVie. Brand name is Viekira Pak® for the co-pack with dasabuvir, and Technivie® for the fixed-dose combination of ombitasvir/paritaprevir/ritonavir *(58,59)*.
- First approved by the US Food and Drug Administration on 24 July 2015
- The combination ombitasvir/paritaprevir/ritonavir/dasabuvir is part of the alternative regimen for genotype 1 infection, and ombitasvir/paritaprevir/ritonavir is the alternative regimen for genotype 4 infection in the 2016 WHO *Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection (53)*.
- AbbVie has not announced an access programme, or a tiered pricing scheme or plans for a voluntary license.
- Beacon has reported that it is at the formulation stage for ombitasvir/paritaprevir/ritonavir.
- Only Malaysia and Ukraine reported prices for dasabuvir + ombitasvir/paritaprevir/ritonavir from AbbVie: US$ 4050 and US$ 2500 per 28-day supply, respectively.
- Information provided in 2016 remains valid. Ombitasvir/paritaprevir/ritonavir is registered in six countries, all high-income countries, except for Egypt. Dasabuvir + ombitasvir/paritaprevir/ritonavir is registered in 38 countries + European Union (EU) countries (65 in total). None of the 38 countries is a low-income country, and only two (Jordan and Tunisia) are lower-middle-income countries.
- For an overall patent situation, please refer to the Medicines Patent Pool database, MedsPaL (http://www.medspal.org).

o AbbVie did not respond in detail to the 2016 or 2017 questionnaires. However, it did provide some information by email in 2016, and sent an email on 25/07/2017 saying the information remained valid for 2017.

4. SOFOSBUVIR

General information

- Therapeutic class: nucleotide analogue inhibitor of NS5B polymerase
- Originator company: Gilead. Sofosbuvir's brand names are Sovaldi® and Virunon® *(60)*.
- First approved by the US Food and Drug Administration on 6 December 2013, and by the European Medicines Agency in January 2014
- Sofosbuvir is part of the preferred regimen for all six major genotypes in the WHO 2016 *Guidelines for the screening, care and treatment of persons with chronic HCV infection (53)*. It is included in the twentieth edition of the WHO *Model list of essential medicines* published in March 2017 (amended in August 2017), and in the 4th Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team (April 2017) *(54, 55)*.
- Sofosbuvir was developed in 1998 by Pharmasset, a biotechnological company founded by scientists from academic institutions, which Gilead acquired in November 2011.
- Optimus Pharma (India), Hetero (India), Mesochem (China), CAD Middle East (Saudi Arabia), Xiamen Halosyntech (China) and Laurus (India) are among the manufacturers of the API, which they sell to finished product manufacturers.

Access, pricing and generic availability information

Access programmes in low- and middle-income countries

The access programme of the innovator company offers access to sofosbuvir, sofosbuvir/ledipasvir and sofosbuvir/velpatasvir mostly through tiered pricing and generic licensing, and limited donations in a few countries. In August 2017, Gilead expanded the licensed territory to include Belarus, Malaysia, Thailand and Ukraine. There are now 105 countries where licensed companies can manufacture and market generic options.

Generic production

Five more companies **(in bold)** were marketing sofosbuvir in 2017: **Beacon**, Beximco, **Cipla**, **Galenica**, Hetero, Incepta, Richmond, Mylan, Natco, Pharco, Pharma 5, **Strides** and **Zydus.** Aurobindo is developing sofosbuvir; as of October 2017, it was at the therapeutic equivalence stage.

Prices reported by the innovator and generic companies and additional information on prices reported by countries

The price offered by Gilead in the countries included in the voluntary license agreements decreased from US$ 300 per bottle (28-day supply) in 2016 to US$ 250 per bottle in 2017. The current price is offered to all countries included in the voluntary license agreement. Information was not available regarding the applicability of that price in Belarus, Malaysia and Thailand. Ukraine had bilaterally negotiated a reduced price with the company. Prices of generic sofosbuvir range from US$ 20 in Pakistan and US$ 24 in Egypt to US$ 728 in Argentina for a 28-day supply (*see* Table A4.1).

Table A4.1 Prices of sofosbuvir 400 mg, per 28-day supply, as reported by companies and countries

Manufacturers	Marketing companies/ distributors	Country of origin	Local market prices		Export prices	
			Public (US$)	Private (US$)	Public (US$)	Private (US$)
Gilead Sciences	Gilead Sciences	United States of America	N/A	N/A	Gilead announced price in countries with voluntary licenses (VL): 250 Prices reported by countries: - VL: 212–250 - Non-VL: 275–2908	Prices reported by countries: VL: 1236–11 200[a] Non-VL: N/A
Laboratorios Richmond	Laboratorios Richmond	Argentina	728	N/A	N/A	N/A
Beacon	Beacon	Bangladesh	N/A	N/A	N/A	N/A
Beximco	Beximco		106	106	N/A	N/A
Incepta Pharmaceuticals Ltd	Incepta Pharmaceuticals Ltd		210	210	210	N/A
Pharco	Pharco[b]	Egypt	24	50	71	N/A
Cipla	Cipla	India	N/A	N/A	N/A	N/A
Hetero Labs	Hetero Labs		N/A	N/A	Price reported in Mongolia 150	N/A
	Abbott India Ltd[c]		N/A	192	N/A	N/A
	Biocon[c]		N/A	125	N/A	N/A
	Dr Reddy's[c]		N/A	215	N/A	N/A
	Sun Pharma[c]		N/A	180	N/A	N/A
Mylan Ltd	Mylan Ltd		N/A	N/A	30[d]	N/A
Natco Pharma Ltd[c]	Natco Pharma Ltd[c]		N/A	149	N/A	N/A
	Emcure Pharmaceuticals Ltd[c]		N/A	154	N/A	N/A
Strides Shasun	Strides Shasun		80	80	30	N/A
Galenica Pharmaceutical Laboratories	Galenica Pharmaceutical Laboratories	Morocco	343	N/A	N/A	N/A
Pharma 5	Pharma 5		274[e]	N/A	N/A	N/A

a The prices of US$ 11 200 and US$ 1236 were reported in Malaysia and Thailand, respectively, in the private sector. These countries were recently included in the licensed territory. The prices are expected to decrease.

b Seventeen other companies distribute sofosbuvir at the same price.

c Natco and some marketing companies of Hetero and Natco products (in parentheses) did not reply to the survey in 2017. Prices are those reported for the 2016 edition. There is no indication that they have halted production/distribution.

d Indicative price reported by Mylan.

e Approximate price due to fluctuating exchange rate. Price applies only to the local market in Morocco.

Regulatory approvals and filings, and WHO-prequalified approvals and submissions

As of June 2017, sofosbuvir from the innovator company is registered in 17 countries in the Gilead licensed territory: Cameroon, India, Indonesia, Nigeria, Tunisia, United Republic of Tanzania and Uzbekistan, in addition to Bolivia, Egypt, El Salvador, Malaysia, Mongolia, Pakistan, Philippines, Rwanda, Thailand[p] and Ukraine (as reported in the 2016 edition).

Additional approvals were obtained in the following countries that are not included in the Gilead licensed territory: Colombia, Ecuador, Peru and Uruguay. Only one additional filing has occurred, in Viet Nam (January 2016). Approval has been pending since 2014 in Kenya, South Africa and Uganda.

Table A4.2. Regulatory approvals and filings of sofosbuvir by the innovator company in 2016 and 2017

2016				2017			
Approved LICs, LMICs, UMICs	Filed LICs, LMICs, UMICs	Approved territory	Filed territory	Approved LICs, LMICs, UMICs	Filed LICs, LMICs, UMICs	Approved territory	Filed territory
20	14	9	8	30	9	17	4

LIC: low-income country; LMIC: lower-middle-income country; UMIC: upper-middle-income country

There were significantly more approvals for sofosbuvir in 2017 compared with 2016, as shown in Table A4.2. In 2017, at least one version of sofosbuvir was registered in 56 countries in total, and at least one generic version of sofosbuvir was available in 48 countries.

Three generic versions of sofosbuvir obtained WHO prequalification (Cipla, Hetero and Mylan). In the 2017 survey, two other companies reported having filed for WHO prequalification (Pharco and Strides), which corresponds to information from WHO showing that there are two dossiers under assessment (*see* Table A4.3). Beacon stated that it plans to submit for prequalification by the end of 2017, although there is no confirmation of that, and Pharma 5 intends doing so in 2018.

Patents

For an overall patent situation, please refer to the Medicines Patent Pool database, MedsPaL (http://www.medspal.org).

Table A4.3. Regulatory approvals and filings of sofosbuvir by generic companies in 2016 and 2017

	2016		2017	
	Approved	Filed	Approved	Filed
Beximco		2	2	
Hetero	6	20	19	32
Incepta			2	34
Pharco			10	7
Strides			13	16
Natco	2	37		
Zydus				7

p Sofosbuvir was registered in Thailand and Ukraine in 2016; at the time, neither country was part of the Gilead licensed territory.

5. SOFOSBUVIR/DACLATASVIR

General information

- Fixed-dose combination of a nucleotide analogue inhibitor of NS5B polymerase (sofosbuvir) and an NS5A inhibitor (daclatasvir), developed or under development by generic manufacturers

- Sofosbuvir/daclatasvir is a recommended preferred regimen for infection with genotypes 1, 3 and 4, and an alternative regimen for infection with genotype 2 in the 2016 WHO *Guidelines for the screening, care and treatment of persons with chronic HCV infection (53)*.

- Sofosbuvir and daclatasvir are included separately the twentieth edition of the WHO *Model list of essential medicines* published in March 2017 (amended in August 2017), but not under the epigraph "fixed-dose combinations". However, sofosbuvir/daclatasvir is listed as a fixed-dose combination in the 4th Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team (April 2017) *(54,55)*.

Access, pricing and generic availability information

Access programmes in low- and middle-income countries

Gilead has signed voluntary license agreements with 10 generic companies, which allows them to market and sell sofosbuvir in 105 countries. BMS has signed a voluntary license with the Medicines Patent Pool, allowing generic companies to sell and market daclatasvir in 112 countries and any country where no patent is in force, under the condition that they do not use BMS technology.

Aurobindo, Cipla, Hetero, Laurus, Mylan and Natco have signed voluntary license agreements with both BMS and Gilead, and therefore can produce and sell sofosbuvir/daclatasvir in the 97 countries that are included in both agreements. They are able to sell in the 15 countries that are included in the BMS voluntary license agreement but not in the Gilead one. This is because the Gilead license prevents selling outside its territory regardless of the patent situation.

In the eight countries that are included in the Gilead voluntary license but not in the BMS one, generic companies can market the regimen if there is no patent on daclatasvir and if they do not use BMS technology. Other companies not included in any of the agreements can sell in any country where there are no patents on either daclatasvir or sofosbuvir. Generic manufacturers produce this combination.

Generic production

Only Beacon (Bangladesh) appears to be marketing a fixed-dose combination currently. The company has not signed any voluntary license agreement and therefore can sell only in countries where neither daclatasvir nor sofosbuvir is patented. In addition, Galenica, Incepta, Pharco and Zydus are at the development stage, and Pharma 5 and Mylan are at more advanced stages. As of November 2017, Beacon had not reported a price. South Africa reported a price of US$ 450 but did not specify the manufacturer.

Beacon did not provide information on registration, but reported that it intended applying for WHO prequalification in late 2017. Mylan, which is in the final stages of development, also plans to apply for WHO prequalification in late 2017.

There is no confirmation that any of these companies applied for WHO prequalification by the end of 2017, which corresponds to information from WHO that there are no dossiers under assessment.

6. SOFOSBUVIR/LEDIPASVIR

General information

- Therapeutic class: nucleotide analogue inhibitor of NS5B polymerase in combination with an NS5A inhibitor
- Originator company: Gilead. The brand name is Harvoni® *(61)*.
- First approved by the US Food and Drug Administration on 10 October 2014. Approved by the European Medicines Agency in November 2014
- Sofosbuvir/ledipasvir is part of the preferred regimen for infection with genotypes 1, 4, 5, 6 in the 2016 WHO *Guidelines for the screening,care and treatment of persons with chronic HCV infection (53)*. It is included the twentieth edition of the WHO *Model list of essential medicines* published in March 2017 (amended in August 2017) and in the 4th Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team (April 2017) *(54,55)*.
- Hetero (India), Mesochem (China), Xiamen Halosyntech (China) and Sequent (India) are among the manufacturers of ledipasvir's API, which they sell to finished product manufacturers.

Access, pricing and generic availability information

Access programmes in low- and middle-income countries

Please refer to the sofosbuvir drug profile (Section 4 of this Appendix) for a brief description of the Gilead access programme.

Generic production

There are four more companies (in **bold**) that now market sofosbuvir in 2017 compared to 2016. In total, the companies are: **Beacon**, **Beximco,** Hetero, Incepta, **Mylan,** (Natco) and **Strides.** In addition, Pharco has sofosbuvir/ledipasvir at formulation stage and Zydus has filed the combination in India.

Prices reported by the innovator and generic companies and additional information on prices reported by countries

The price offered by Gilead in countries included in the voluntary license agreements decreased from US$ 400 per bottle (28-day supply) in 2016 to US$ 300 in 2017. There is still no information regarding the application of these prices in the recently included countries of Belarus, Malaysia and Thailand. Ukraine was also included recently but was already benefiting from reduced prices following bilateral negotiations. Prices reported by generic companies for a 28-day supply of sofosbuvir/ledipasvir range from US$ 75 to US$ 364 (*see* Table A6.1).

Table A6.1. Prices of sofosbuvir + ledipasvir 400 mg + 90 mg, per 28-day supply, as reported by companies and countries

Manufacturers	Marketing companies/ distributors	Country of origin	Local market prices		Export prices	
			Public (US$)	Private (US$)	Public (US$)	Private (US$)
Gilead Sciences	Gilead Sciences	United States of America	N/A	N/A	Gilead announced price in countries with voluntary licenses (VL): 300 Prices reported by countries: VL: 280–680 Non-VL: 440	Prices reported by countries VL: 1648–14 227[a] Non-VL: N/A
Beacon	Beacon	Bangladesh	N/A	N/A	N/A	N/A
Beximco	Beximco		364	364	"Price is negotiable with potential partner to increase access to medication"	
Incepta Pharmaceuticals Ltd	Incepta Pharmaceuticals Ltd		350	350	350 Price reported in Uzbekistan: 157	N/A
Hetero Labs	Hetero Labs	India	N/A	N/A	N/A	N/A
Mylan Ltd	Mylan Ltd		N/A	N/A	75[b] Prices reported in Cameroon, Mongolia and Viet Nam: 143, 250 and 594, respectively	N/A
Natco Pharma Ltd[c]	Natco Pharma Ltd[c]		N/A	149	N/A	N/A
	Emcure Pharmaceuticals Ltd[c]		N/A	154	N/A	N/A
Strides Shasun	Strides Shasun		110	110	100	N/A

a Prices of US$ 14 227 and US$ 1648 were reported in Malaysia and Thailand, respectively, in the private sector. These countries were recently included in the licensed territory. The prices are expected to decrease in the near future.

b Indicative price reported by Mylan.

c Natco did not reply to the survey in 2017. Prices are those reported for the 2016 edition. There is no indication that the company has halted production or distribution.

Regulatory approvals and filings, and WHO-prequalified approvals and submissions

As of June 2017, Gilead had obtained market authorization in 14 countries in its license territory, compared to three in 2016. Approvals were obtained in Bolivia, Morocco, Thailand and Tunisia. In some of the countries, regulatory approval has not progressed for some time (e.g. India, Indonesia, Kenya, Philippines and Uganda were reported as filing in both 2016 and 2017) (*see* Table A6.2).

Table A6.2. Regulatory approvals and filings of sofosbuvir/ledipasvir by the originator company in 2016 and 2017

2016				2017			
Approved LICs, LMICs, UMICs	Filed LICs, LMICs, UMICs	Approved territory	Filed territory	Approved LICs, LMICs, UMICs	Filed LICs, LMICs, UMICs	Approved territory	Filed territory
9	11	3	11	25	13	14	9

LIC: low-income country; LMIC: lower-middle-income country; UMIC: upper-middle-income country

There were significantly more approvals and filings for sofosbuvir/ledipasvir in 2017 compared to 2016. Seventeen low-, lower-middle- and upper-middle-income countries have now registered at least one generic version of sofosbuvir/ledipasvir (including Cambodia, Chad, Côte d'Ivoire, Gabon, Guinea, India, Kyrgyzstan, Myanmar, Tajikistan, Turkmenistan and Uzbekistan) (*see* Table A6.3). If countries where Gilead products received regulatory approval are included, the total number of countries with at least one approved version of sofosbuvir/ledipasvir rises to 36, including three countries (Brazil, China and Egypt) that rank among the 10 countries with the highest burden of HCV globally.

None of the generic companies that market sofosbuvir/ledipasvir has obtained WHO prequalification or filed a dossier. Beacon, Hetero, Mylan and Strides said they plan to submit a dossier to WHO Prequalification Programme in the near future.

Patents

For information on the overall patent situation, please refer to the Medicines Patent Pool database, MedsPaL (http://www.medspal.org) *(29)*.

Table A6.3. Regulatory approvals and filings of sofosbuvir/ledipasvir by generic companies in 2016 and 2017

	2016		2017	
	Approved	Filed	Approved	Filed
Beximco			1	
Hetero	4		10	38
Incepta			2	30
Strides			4	14
Natco	1			

7. SOFOSBUVIR/VELPATASVIR

General information

- Therapeutic class: fixed-dose combination of a nucleotide analogue inhibitor of NS5B polymerase (sofosbuvir) and an NS5A inhibitor (velpatasvir)
- Originator manufacturer: Gilead. The brand name of sofosbuvir/velpatasvir is Epclusa® *(62)*.
- First approved by the US Food and Drug Administration on 26 June 2016, and by the European Medicines Agency on 28 July 2016, with an indication for the treatment of adult patients with chronic HCV infection with genotypes 1, 2, 3, 4, 5 or 6 (pangenotypic).
- The WHO 2016 *Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection* are being revised *(53)*. WHO plans to release updated guidelines in 2018 to promote the transition to newer, more effective medicines, particularly pangenotypic DAA regimens that are effective for all six major genotypes of HCV.
- Sofosbuvir/velpatasvir 400 mg + 100 mg tablet is included in the twentieth edition of the WHO *Model list of essential medicines* published in March 2017 (amended in August 2017), and is published in the 4th Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team (April 2017) *(54,55)*.
- Mesochem (China), Hetero (India), Xiamen Halosyntech Co. Ltd (China) and Strides (India) manufacture the API (velpatasvir) and market it to finished product manufacturers.

Access, pricing and generic availability information

Access programmes in low- and middle-income countries

Please refer to the sofosbuvir drug profile (*see* Section 4 in this Appendix) for a brief description of the Gilead access programme. Gilead is yet to announce a price for countries in the licensed territory for sofosbuvir/velpatasvir.

Generic production

Beacon, Hetero, Incepta, Mylan and Strides reported marketing the product. Beximco and Zydus are developing it and are at the formulation stage. In addition, Aurobindo and Pharco plan to start development soon. In 2016, none of these companies reported that they were developing velpatasvir.

Prices reported by generic companies and by Gilead, and additional information on prices reported by countries are given in Table A7.1.

Table A7.1. Prices of sofosbuvir/velpatasvir 400 mg + 100 mg, per 28-day supply, as reported by companies and countries

Manufacturers	Marketing companies/ distributors	Country of origin	Local market prices		Export prices	
			Public (US$)	Private (US$)	Public (US$)	Private (US$)
Gilead Sciences	Gilead Sciences	United States of America	N/A	N/A	Gilead did not announce price in countries with a voluntary license (VL)[q] Price reported in South Africa: 550	N/A
Beacon	Beacon	Bangladesh	N/A	N/A	N/A	N/A
Incepta Pharmaceuticals Ltd	Incepta Pharmaceuticals Ltd		N/A	N/A	N/A	N/A
Hetero Labs	Hetero Labs	India	N/A	N/A	N/A	N/A
Mylan Ltd	Mylan Ltd		N/A	N/A	125[a]	N/A
Strides Shasun	Strides Shasun		130	130	130	N/A

a Indicative price reported by Mylan

Regulatory approvals and filings, and WHO-prequalified approvals and submissions

No filings were reported by the originator. Generic versions of sofosbuvir/velpatasvir are registered in very few countries, and until very recently, few generic companies produced the regimen. As of mid-2017, it was registered only in Cambodia and India (Hetero) and in Uzbekistan (Incepta), according to the survey responses from generic companies. None of the five generic companies that market sofosbuvir/velpatasvir have obtained WHO prequalification or filed a dossier. Three companies (Beacon, Hetero and Mylan) reported that they plan to submit a dossier in the near future.

Patents

For information on the overall patent situation, please refer to the Medicines Patent Pool database, MedsPaL (http://www.medspal.org).

q Since August 2017, 105 countries are part of the voluntary license agreement. However, there is no confirmation regarding "flat" pricing in the four newly included countries (Belarus, Malaysia, Thailand and Ukraine).

8. SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR

- Therapeutic class: fixed-dose combination of sofosbuvir, an HCV nucleotide analogue NS5B polymerase inhibitor; velpatasvir, an HCV NS5A inhibitor; and voxilaprevir, an HCV NS3/4A protease inhibitor
- Originator manufacturer: Gilead. The brand name is Vosevi® *(63)*.
- Approved by the US Food and Drug Administration on 18 July 2017 and by the European Medicines Agency on 28 July 2017
- Indication: treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis
- The combination is not included in the twentieth edition of the WHO *Model list of essential medicines* published in March 2017 (amended in August 2017), and not published in the 4th Invitation to submit an Expression of Interest to the WHO Prequalification Team (April 2017) for product evaluation *(54,55)*.
- Gilead has not made public any information regarding the regimen's inclusion in access and pricing programmes or in the voluntary license agreement. Please refer to the sofosbuvir drug profile (*see* Section 4 in this Appendix) for a brief description of the Gilead access programme.
- There are no generic versions. Beacon has announced that they have started development. Beximco, Hetero, Mylan, Strides and Zydus plan to develop generic versions.
- For an overall patent situation, please refer to the Medicines Patent Pool database, MedsPaL (http://www.medspal.org).

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ANNEXES

ANNEX 1. PRICES OF HCV DIAGNOSTICS

The information in this table is drawn from *Putting HIV and HCV to the test, third edition.* Geneva: Médecins Sans Frontières; 2017.

Products in bold are WHO-prequalified (as of December 2017).

	Product	Manufacturer	Technology	Min price (US$)	Max price (US$)
HCV testing	**SD Bioline**	Standard Diagnostics Korea	RDT (Ab)	1	
	OraQuick	OraSure	RDT (Ab)	7	
Confirmatory testing	**GeneXpert**	Cepheid	near-POC	13	18
	Genedrive	Genedrive	near-POC	25	30
	Truelab/Truenat	Molbio Diagnostics	POC	20	
	Architect	Abbott	NAT	25	50
	Generic	Biocentric	NAT	23	
	Aptima	Hologic	NAT	10	25
	CAP/CTM HCV	Roche	NAT	35	45
	Versant HCV	Siemens	NAT	72	100
Test-of-cure	Truelab/Truenat	Molbio Diagnostics	POC	20	
	RealTime	Abbott	NAT	11	23
	Generic	Biocentric	NAT	23	
	Aptima	Hologic	NAT	10	25
	Artus HCV	Qiagen	NAT	16	45
	Versant HCV	Siemens	NAT	72	100

	Min price (US$)	Max price (US$)
Price per patient (HCV testing + confirmatory testing + test-of-cure)	22	207

Ab: antibody; HCV: hepatitis C virus; NAT: nucleic acid test; POC: point of care; RDT: rapid diagnostic test

ANNEX 2. LOW- AND MIDDLE-INCOME COUNTRIES AND AREAS NOT INCLUDED IN VOLUNTARY LICENSE AGREEMENTS

The shaded sections denote low- and middle income countries and territories that are currently not included in the voluntary license agreements. Countries in bold are among the 20 countries with the highest burden of HCV infection globally.

Region of the Americas	Income category	BMS VL	Gilead VL
Argentina	UMIC	NO	NO
Belize	UMIC	YES	NO
Brazil	UMIC	NO	NO
Colombia	UMIC	NO	NO
Costa Rica	UMIC	YES	NO
Dominican Republic	UMIC	YES	NO
Ecuador	UMIC	YES	NO
Grenada	UMIC	YES	NO
Jamaica	UMIC	YES	NO
Mexico	UMIC	NO	NO
Panama	UMIC	YES	NO
Peru	UMIC	NO	NO
Saint Lucia	UMIC	YES	NO
Venezuela (Bolivarian Republic of)	UMIC	NO	NO
Eastern Mediterranean Region	**Income category**	**BMS VL**	**Gilead VL**
Egypt	LMIC	NO	YES
Iran (Islamic Republic of)	UMIC	NO	NO
Iraq	UMIC	YES	NO
Jordan	LMIC	NO	NO
Lebanon	UMIC	NO	NO
Syrian Arab Republic	LMIC	YES	NO
West Bank and Gaza Strip	LMIC	YES	NO
Yemen	LMIC	YES	NO

European Region	Income category	BMS VL	Gilead VL
Azerbaijan	UMIC	YES	NO
Albania	**UMIC**	**NO**	**NO**
Armenia	LMIC	NO	NO
Belarus	UMIC	NO	YES
Bosnia and Herzegovina	UMIC	NO	NO
Bulgaria	UMIC	NO	NO
Croatia	UMIC	NO	NO
Georgia	LMIC	YES	NO
Kazakhstan	UMIC	NO	NO
Kosovo (in accordance with Security Council resolution 1244 (1999))	LMIC	NO	NO
Kyrgyzstan	LMIC	NO	YES
Montenegro	UMIC	NO	NO
Republic of Moldova	LMIC	NO	NO
Romania	UMIC	NO	NO
Russian Federation	UMIC	NO	NO
Serbia	UMIC	NO	NO
Tajikistan	LMIC	NO	YES
The former Yugoslav Republic of Macedonia	UMIC	NO	NO
Turkey	UMIC	NO	NO
Ukraine	LMIC	NO	YES
South-East Asia Region	**Income category**	**BMS VL**	**Gilead VL**
Thailand	UMIC	NO	YES
Western Pacific Region	**Income category**	**BMS VL**	**Gilead VL**
China	UMIC	NO	NO
Malaysia	UMIC	NO	YES

LMIC: lower-middle-income country; UMIC: upper-middle-income country; VL: voluntary license

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