Accelerating access to hepatitis C diagnostics and treatment

Overcoming barriers in low- and middle-income countries

Global progress report 2020

World Health Organization

Accelerating access to hepatitis C diagnostics and treatment

Overcoming barriers in low- and middle-income countries

Global progress report 2020

World Health Organization

Accelerating access to hepatitis C diagnostics and treatment: overcoming barriers in low and middle-income countries. Global progress report 2020

ISBN 978-92-4-001900-3 (electronic version)

ISBN 978-92-4-001901-0 (print version)

Suggested citation. Accelerating access to hepatitis C diagnostics and treatment: overcoming barriers in low and middle-income countries. Global progress report 2020. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Layout by 400 Communications.

Contents

Acknowledgements

This publication was developed jointly by the Global HIV, Hepatitis and STIs Programmes (HHS) and the Division on Access to Medicines and Health Products (MHP) of the World Health Organization (WHO). The process was led by Françoise Renaud and Erika Dueñas Loayza, and coordinated by Daniel Low-Beer and Clive Ondari. The contributions of Fernando Pascual Martinez, who managed the data collection and conducted the interviews, Emmanuel Fajardo who conducted research on diagnostics, and Parijat Baijal, who was the lead writer, are gratefully acknowledged.

We particularly thank colleagues in ministries of health and in WHO regional and country offices for their contributions, as well as Fuqiang Cui, Boniface Dongmo Nguimfack, Philippa Easterbrook, Olufunmilayo Lesi, Niklas Luhmann, Gilles Forte, Kiu Siang Tay, Adriana Velazquez Berumen, Deusdedit Mubangizi, Maria Mercedes Perez Gonzalez, Irena Prat, Anita Sands, Dzintars Gotham and Nicole Homb from WHO headquarters. Bandana Malhotra edited the report.

We are grateful to Meg Doherty, Minghui Ren and Mariângela Simão for their overall support and leadership.

The following persons were interviewed for the report: François Bompart (Drugs for Neglected Diseases *initiative,* Switzerland), Esteban Burrone (Medicines Patent Pool, Switzerland), Jessica Burry (Médecins Sans Frontières, Switzerland), Jean Michel Caudron (United Nations Development Programme, Switzerland), Lorena Di Giano (Redla Red Latinoamericana por el Acceso a Medicamentos), Khalil Elouardighi (Coalition PLUS, Paris), Gamal Esmat (Cairo University, Egypt), Charles Gore (Medicines Patent Pool, Switzerland), Andrew Hill (University of Liverpool, United Kingdom), Priti Krishtel (I-Mak, United States), Vidhi Lohia (Clinton Health Access Initiative), Pauline Londeix (Observatoire pour la Transparence, France), Cécile Macé (United Nations Development Programme, Switzerland), Craig McClure (Clinton Health Access Initiative), Leena Menghaney (Médecins Sans Frontières, India), Othoman Mellouk (International Treatment Preparedness Coalition, Morocco), Ellen ‘t Hoen (Medicines Law & Policy, The Netherlands), Karin Timmermans (Unitaid, Switzerland), Pedro Villardi (Grupo de Trabalho sobre Propriedade Intelectual, Brazil), Marcela Vieira (Graduate Institute, Switzerland), Ernst Wisse (Médecins du Monde, France). We are also grateful to colleagues in Unitaid and Clinton Health Access Initiative for their comments during the finalization of the report.

Financial acknowledgments

Funding support for the development of the report was kindly provided by Unitaid. WHO also thanks the other institutions that provided staff time and made other contributions to the production of the report.

Abbreviations and acronyms

APH	Alliance for Public Health Ukraine
API	active pharmaceutical ingredient
APRI	aspartate aminotransferase-to-platelet ratio index
BMS	Bristol-Myers Squibb
CHAI	Clinton Health Access Initiative
COVID-19	coronavirus disease 2019
DAA	direct-acting antiviral (medicine)
DCV	daclatasvir
DND*i*	Drugs for Neglected Diseases *initiative*
EASL	European Association for the Study of the Liver
EMA	European Medicines Agency
EPO	European Patent Office
ERP	Expert Review Panel
FAS	Federal Antimonopoly Service (Russian Federation)
FIND	Foundation for Innovative New Diagnostics
Global Fund	the Global Fund to Fight AIDS, Tuberculosis and Malaria
GNI	gross national income
G/P	glecaprevir/pibrentasvir
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IVD	in vitro diagnostics
LDV	ledipasvir
MDM	Médecins du Monde
MSF	Médecins Sans Frontières
MoH	Ministry of Health
MPP	Medicines Patent Pool
MSM	men who have sex with men
NAT	nucleic acid testing
PCR	polymerase chain reaction
POC	point of care
PWID	people who inject drugs
RDT	rapid diagnostic test
RNA	ribonucleic acid
SDGs	Sustainable Development Goals
STI	sexually transmitted infection
TB	tuberculosis
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UNDP	United Nations Development Programme
USA	United States of America
US FDA	United States Food and Drug Administration
WHO	World Health Organization

© WHO/NOOR/Sebastian Liste

Executive summary

The 2020 global report on access to hepatitis C diagnostics and treatment is being published at **an unprecedented time for global health.** The data presented in this report were collected in 2019. Since then, the coronavirus disease (COVID)-19 pandemic has spread to countries and populations worldwide, resulting in 79 million infections and about 1.7 million deaths by end December 2020. Many countries are already facing major disruptions to essential health services. They risk a reversal of decades of progress in health and development. The pandemic is a strong reminder that we need to continue to invest in building resilient health systems for universal health coverage and respond to emergencies. It is also an urgent call to maintain the momentum towards achieving the goals of the 2030 Agenda for Sustainable Development.

This is the third World Health Organization (WHO) global report on access to hepatitis C treatment, following the reports in 2016 and 2018. For the first time, the 2020 report also includes information on hepatitis C diagnostics. The report focuses on 12 countries that represent a combination of high disease burdens and successful public health approaches. It provides updates on the diverse landscape of national strategies and market conditions, which together shape a country's response to viral hepatitis. The report demonstrates how programmes in different settings are achieving greater affordability, quality, equity and efficiency in scaling up hepatitis C diagnostics and treatment. The practical lessons and examples illustrate how all countries can further simplify, decentralize and expand service delivery to achieve universal coverage.

The global response to hepatitis C is positioned for "take-off" for a decade of acceleration towards the goals of the 2030 Agenda for Sustainable Development. Following the adoption of the first Global Health Sector Strategy on Viral Hepatitis 2016–2021, a number of countries have made impressive gains supported by government commitment, national strategic plans, simplified guidelines, greater availability of quality-assured diagnostics and treatment options, and continued price reductions. While less than 20 countries had national viral hepatitis strategic plans in 2012, this had increased to 124 countries by 2018. In the 12 countries highlighted in this report, eight have comparable yearly data on access to hepatitis C treatment. The data showed that the cumulative number of people receiving hepatitis C treatment grew more than 20-fold between 2015 and 2018 – from about 122 000 patients at the end of 2015 to more than 2.6 million by the end of 2018.

Some champion countries are leading the way and have contributed massively to the recent scale up. Egypt, one of the countries with the largest burden of hepatitis C infection in the world, has made significant advances since 2018 towards hepatitis C elimination through a large countrywide public health effort to screen the entire population aged 18 years and older (a target population of 62.5 million) and link those in need to care. Nearly 50 million adults and 9 million children aged 12–18 years were screened, and 1.5 million additional persons had started treatment by mid-2019. This constitutes one of the largest public health efforts to date towards hepatitis C elimination in low- and middle-income countries. Egypt now plans to support other countries in the sub-Saharan African region in their scale up efforts. Other countries such as Georgia, Mongolia, Pakistan and Rwanda have also greatly expanded their outreach in the past couple of years. The **common factors for the success of the public health response in these countries** include strong political commitment, widespread testing, and a comprehensive strategy to deliver services through an integrated approach within the framework of universal health coverage. Countries have leveraged existing health infrastructure and the experience of programmes such as HIV to expand hepatitis screening and testing services, and seized opportunities to address patent- and regulation-related challenges specific to the country context. They have also leveraged domestic financing, generic competition and pricing reduction, and worked alongside civil society to advocate for reduced prices and support access for those most at risk and vulnerable. Important lessons can be learned from the experiences of these countries.

The WHO 2017 guidelines on hepatitis B and C testing, and the WHO 2018 guidelines for the screening, care and treatment of persons with chronic HCV infection provide a timely opportunity to accelerate access. These guidelines introduced major simplifications in the delivery of testing (screening and diagnosis) and treatment services within a public health approach. The goal of hepatitis C treatment is cure. The guidelines included a simplified two-step testing strategy to diagnose chronic hepatitis C virus (HCV) infection. A "treat all" approach with prompt treatment initiation is taken for all people living with chronic HCV infection – defined as those with active viraemic infection (with the exception of pregnant women and children under 12 years) – with direct-acting antiviral (DAA) drugs that can cure more than 95% of cases with chronic HCV, thereby reducing the risk of death from cirrhosis or liver cancer. The guidelines recommend the use of three pangenotypic regimens, which can treat all strains of HCV without the need for additional specialized genotyping, and WHO is supporting countries to transition to these new regimens. In addition, the updated guidelines also provide key good practice approaches to support simplified service delivery across the continuum of care.

The sources of quality-assured generic direct-acting antivirals and diagnostics are steadily increasing. In 2016, there were no generic DAAs that were WHO-prequalified or approved by a stringent regulatory authority. By 2020, six generic manufacturers had at least one DAA prequalified by WHO. By the end of 2020, a WHO-prequalified fixed-dose combination of sofosbuvir/daclatasvir was available from a generic supplier. In-country product registrations are also increasing. In 2019, a total of 62 low- and middle-income countries had registered at least one version of sofosbuvir and daclatasvir, sofosbuvir/ledipasvir or sofosbuvir/velpatasvir from the originator or generic manufacturers, as compared to 32 in 2017. Similarly, only one HCV rapid diagnostic test and a line immunoassay were prequalified in 2016. By 2020, four molecular HCV assays and eight serology assays were WHO-prequalified.

Prices of DAAs continue to fall, supported by increased generic competition. Low- and middle-income countries can now aim to achieve a price as low as US$ 60 per patient for a 12-week course of treatment with WHO-prequalified generic sofosbuvir and daclatasvir, one of the lowest reported prices for WHO-prequalified generic hepatitis C medicines to date. Between 2016 and 2018, the lowest reported price per 28-day supply of sofosbuvir dropped by 75% from US$ 60 to US$ 15, and for daclatasvir by 60% from US$ 15 to US$ 6; both reported from India for the domestic market for WHO-prequalified products.

Prices have also dropped for the generic fixed-dose combination of sofosbuvir/daclatasvir, which has become the pangenotypic regimen of choice for most countries, given its favourable pricing and the availability of several pre-qualified products. A WHO-prequalified generic fixed-dose combination of sofosbuvir/daclatasvir was available in India for US$ 23 per 28-day supply or US$ 69 per course of treatment. Some generic manufacturers who are not yet WHO-prequalified are reporting even lower prices. Generic sofosbuvir/daclatasvir was available for US$ 16 per 28-day supply or US$ 48 per course of treatment from a local manufacturer in Egypt and for US$ 7–10 per 28-day supply or US$ 25 per course of treatment from a local manufacturer in Pakistan. However, many countries are not benefiting from these prices, and large variations in prices and patent barriers continue to persist among countries. Prices in upper-middle-income countries remain a major barrier to scale up.

The availability and affordability of diagnostics remains a major barrier to treatment scale up, in particular, in low- and middle-income countries. Information on the pricing of HCV in vitro diagnostics (IVDs) is limited, and the market is dominated by a small number of companies. In 2020, prices offered by suppliers of WHO-prequalified HCV rapid diagnostic tests ranged between US$ 1 and US$ 8 per test, yet many countries are not accessing rapid diagnostic tests at these low prices.

© WHO/NOOR/Sebastian Liste

Laboratory-based immunoassays were offered at a price between US$ 1 and US$ 2. Reagents for nucleic acid testing (NAT) that can be used at the point of care (POC) to detect HCV RNA cost between US$ 14 and US$ 30, plus the fixed costs of the analyser itself, which ranges from US$ 10 000 to US$ 25 000. High-throughput laboratory-based analysers can cost over US$ 100 000, with reagents costing between US$ 9 and US$ 50 per test. Manufacturers of diagnostic platforms/analysers are offering various pricing schemes, such as reagent rental and leasing agreements. However, many low- and middle-income countries with nascent screening programmes and low testing volumes have not been able to fully benefit from these schemes and leverage existing infrastructure. As hepatitis C treatment becomes more affordable and widely available, expanding access to simple, affordable and quality-assured hepatitis C IVDs is much needed so that countries can screen large numbers of people, identify patients in need of treatment and provide appropriate care.

Efforts to address patent-related barriers are making products more accessible but there are still obstacles to be overcome. In a major step towards expanding access to glecaprevir/pibrentasvir, a voluntary license agreement was signed at the end of 2018 between the originator company AbbVie and the Medicines Patent Pool (MPP). This enables generic manufacturer partners in low- and middle-income countries and areas to develop and supply a quality-assured pangenotypic combination, making this drug regimen more accessible. However, many upper-middle-income countries are not included in this agreement, and neither is India. AbbVie has signed a licensing agreement with one generic manufacturer; however, generic production of glecaprevir/pibrentasvir had not yet started as of mid-2020. For daclatasvir, BMS announced in early 2020 that the marketing authorizations for its originator product will be withdrawn or will be allowed to lapse in countries where the product is no longer routinely prescribed or where there are other therapeutic options available. Following the withdrawal/lapse of the marketing authorization, the patents in those countries will also be allowed to lapse and will not be enforced in the interim period. This decision has an important impact on access to daclatasvir, with 26 additional countries, including some outside the licensed territory to the MPP, now having access to generic daclatasvir, with or without existing patents. For sofosbuvir, ledipasvir and velpatasvir, the number of countries included in the voluntary licensing agreement of Gilead has remained unchanged, and many high-burden countries remain excluded. For diagnostics, the role of patent protection is often more complex than it is for medicines, because many different constituents of IVDs and the technique may be patented.

Despite recent achievements in many areas, the overall global landscape of access to hepatitis C diagnostics and treatment remains uneven and fragmented. The progress achieved to date is fragile, and access to hepatitis C testing and treatment is yet to reach sufficient levels of coverage to attain the global goal of eliminating viral hepatitis as a major public health threat by 2030. Globally, at the end of 2017, only 5 million – or 7% – of the 71 (62–79) million people chronically infected with HCV had cumulatively received treatment with DAAs. Access to hepatitis C diagnosis and treatment remains low in many low- and middle-income countries with a high disease burden, and not all countries have been able to equally avail of opportunities to address barriers related to pricing, patents, product regulation and demand creation. The COVID-19 pandemic may not only slow down progress but may also reverse the gains.

Importantly, the population groups that are most at risk of hepatitis C infection continue to be underserved in access to services, and data on coverage in these groups are lacking. A WHO desk review in 2019 of 81 national hepatitis policies and plans found that less than half of them outlined the necessary harm reduction and hepatitis C testing and treatment interventions for people who inject drugs, in accordance with the Global Health Sector Strategy on Viral Hepatitis. Global targets will not be met without massively accelerating universal access to hepatitis C testing, treatment and prevention services for people who inject drugs, people in prisons, men who have sex with men, and other vulnerable groups; and leveraging synergies with related services such as those for HIV prevention, treatment and care, and substance use.

As countries continue to tackle the disease burden and service disruptions caused by the COVID-19 pandemic, it is critical to ensure that the recent momentum and gains in the response to hepatitis C are not lost. Global efforts to scale up access to high-impact interventions for hepatitis C through a public health approach must be sustained and accelerated in the coming decade, as part of broader efforts towards universal health coverage.

The key priorities include:

- **accelerating universal access to hepatitis C IVDs** that can be used at or near the POC for all through decentralization of screening and diagnostic services, task-sharing, simplifications in sample transportation and service delivery, integration with existing infrastructure, leveraging multidisease diagnostic platforms, obtaining more favourable prices, pooling procurement across diseases and fostering demand creation;
- **continuing to pursue comprehensive strategies for more affordable hepatitis C diagnostics and treatment across all country income categories;** including through addressing patent-related barriers and public health-oriented licensing, and generic manufacturing of quality-assured medicines. Other strategies are price–volume negotiations with manufacturers to create high volume, low costs and high-value markets, including value-for-money reagent rental agreements for HCV NAT platforms. Access should be promoted through market intelligence and greater market transparency, patent oppositions, generic competition and leveraging efficient procurement processes;
- **leaving no one behind in line with the SDGs,** by ensuring universal health coverage inclusive of key, underserved and overlooked populations, such as people who inject drugs, people in prisons, migrant and refugee populations, men who have sex with men, people living with HIV with comorbidities and other vulnerable groups; investing in data and targets that account for progress in these groups; and engaging communities in planning and decision-making;
- **facilitating product registration** of quality-assured recommended DAAs with national regulatory authorities through approaches such as leveraging the WHO Collaborative Procedure for Accelerated Registration, or using drug waivers – supported by documentation related to WHO prequalification – to expedite access while in the process of obtaining full registration. This would ensure rapid in-country availability of diagnostic and treatment commodities, increase competition, lower prices and minimize service disruptions;
- seeking greater **financing options,** in particular, by leveraging domestic financing as part of integrated public health approaches and universal health coverage packages in low- and middle-income countries with varying disease burdens. Opportunities provided by existing international funding mechanisms such as The Global Fund should also be built on for synergistic interventions;
- **leveraging synergies across the health sector,** such as through the use of multidisease diagnostic platforms/analysers (including NAT platforms for use at POC), common service delivery platforms (e.g. harm reduction for HIV and viral hepatitis), facilitating integration of hepatitis commodities into existing national procurement and supply mechanisms of essential medicines, and using common approaches to strengthening person-centred data systems and human resources for health.

I Introduction

The global public health response to the hepatitis C virus (HCV) is ready for a decade of acceleration towards the Sustainable Development Goals (SDGs). The introduction of direct-acting antiviral (DAA) medicines in 2014 with high cure rates, shorter treatment durations, fewer side-effects and simplified delivery as compared to previous medicines, revolutionized the treatment of HCV and provided an unprecedented opportunity for widespread scale up. The prices of these drugs, initially prohibitive for many countries, have continued to drop dramatically as low-price generic treatments become more widely accessible. An increasing number of countries are developing national plans and leveraging opportunities to mobilize and allocate resources, and more people are receiving life-saving diagnostic and treatment services for HCV than ever before.

Yet the coverage of these services worldwide remains low and uneven, and major gaps remain. At the end of 2017, only 5 million – or 7% – of the 71 (62–79) million people chronically infected with HCV had received treatment with DAAs *(1)*. Updated data will be available in the course of 2021. Some of the persistent challenges include the lack of large-scale access and implementation of simplified and affordable diagnostics, slow progress in expanding registration and availability of quality-assured products, gaps in data, inadequate availability of harm reduction and prevention services for key populations, and weak health systems overall.

This report provides an update on the recent progress achieved in scaling up the response to HCV in low- and middle-income countries (Boxes 1 and 2). It is the third World Health Organization (WHO) global report on the status of access to hepatitis C treatment, following the reports of 2016 and 2018. Further, for the first time, this year's report includes information on hepatitis C diagnostics. With a focus on selected countries with diverse HCV epidemics, the report provides updates on the various dimensions of access to HCV diagnostics and pharmaceutical products, including product pricing, the regulatory environment and patent status, which together shape the national hepatitis response in different settings. It highlights how national programmes are scaling up WHO-recommended public health approaches towards universal access, adapted to their national contexts, to overcome barriers and achieve greater affordability, quality, equity and efficiency in their responses.

The 2020 report is being published at an unprecedented time for global health. The data presented in this report were collected in 2019. Since then, the coronavirus disease (COVID)-19 pandemic has resulted in 79 million infections and about 1.7 million deaths worldwide by end December 2020 *(2)*. Many countries are facing disruptions in essential health services. In a survey conducted by WHO between April and June 2020, a limited but significant number of 12 low- and middle-income countries reported disruptions in the delivery of HCV diagnosis and treatment services, including potential stock-outs of key supplies. Other data from partners indicate similar challenges, with a drop of 50% in HIV testing and up to 75% in TB case notifications in some places by June 2020 *(3)*. The vast health and human impact of the pandemic can jeopardize, or even reverse, decades of progress in health and development. Yet, at the same time, 2020 is a key year when low- and middle-income countries are ready for a decade of acceleration towards the SDGs. Against this backdrop, this report is a strong reminder that we need to continue to invest in building resilient and sustainable health systems that are focused on universal health coverage.

Box 1
Methodology

The data presented in this report were compiled from a number of available sources.

Data from selected countries. In 2019, WHO conducted a survey among selected low- and middle-income countries that represent a combination of high disease burdens and recent successful public health responses. This report presents information on the access strategies, service coverage, prices, patents and regulatory status gathered in these countries: Brazil, China, Egypt, Georgia, India, Malaysia, Mongolia, Morocco, Pakistan, Russian Federation, Rwanda, Ukraine. These countries face a common urgent need to address their HCV epidemics in a diverse range of country contexts. Each of these countries is implementing a public health approach to enhance access to hepatitis C services through various strategies in response to their specific country realities, and they were selected to highlight their efforts to address ongoing barriers. The experiences of these countries can provide valuable inputs to other low- and middle-income countries as they scale up their programmes, fostering exchange of experiences among countries and greater market transparency. Examples from additional countries, including high-income countries, are also included where relevant.

Information from manufacturers. The WHO survey also gathered data on pricing, licensing and regulatory status from the three main originator companies (Gilead, Bristol-Myers Squibb [BMS] and AbbVie) and 31 generic companies producing DAAs for HCV treatment. Excluding non-responses and incomplete information, data from two originator companies and 16 generic companies were considered for inclusion in this report, complemented by other published sources where relevant. Information on diagnostics was compiled from the ongoing technical work of WHO in this area. It should be noted that inclusion of supplier information in this report does not imply any judgement from WHO regarding the quality of their products.

Inputs from technical and civil society partners. Qualitative inputs were gathered from interviews with 20 key informants representing technical expertise from international organizations, academic institutions and nongovernmental organizations engaged in the global HCV response. Additional information from global partners and from the scientific literature was included where relevant.

Global disease burden estimates. Global estimates of the prevalence and incidence of, and mortality from HCV are based on the 2017 WHO Global hepatitis report *(1)*. These data will be updated in 2021.

The data from countries and manufacturers presented in this report were collected mostly during 2019. Since then, the challenges posed by the COVID-19 pandemic have caused service disruptions to many health services. Where available, updated data from early 2020 are also included in the report.

Box 2
Outside the scope of this report – hepatitis A, B, D and E

There are five main strains of the hepatitis virus, referred to as types A, B, C, D and E. All strains cause liver disease but differ in relation to the disease burden, modes of transmission, severity of illness, geographical distribution, and available prevention and treatment options.

Together, these viruses account for an estimated 1.4 million deaths per year, one of the major infectious disease burdens. Of these, the two major strains of the hepatitis virus, hepatitis B and C, are responsible for 95% of mortality (47% and 48%, respectively) *(1)*. The WHO Global Health Sector Strategy on Viral Hepatitis 2016–2021, the first comprehensive global strategy for addressing viral hepatitis, sets targets for the elimination of both hepatitis B and hepatitis C viruses as public health threats by 2030; with a 90% reduction in new cases of chronic viral hepatitis B and C infections, and a 65% reduction in viral hepatitis B and C deaths, by 2030 *(4)*.

Considerable progress has been made in recent years towards achieving elimination of the hepatitis B virus, in particular, through vaccines that are safe, available and effective. The scale up of the delivery of hepatitis B vaccination through universal infant hepatitis B immunization, including with the delivery of a birth dose, has been highly effective in reducing new infections in children and the burden of new chronic HBV. The global coverage of routine infant immunization with this vaccine (third dose) was 84% in 2017. In many countries where 8–15% of children used to become chronically infected with the hepatitis B virus, vaccination has reduced the rate of chronic infection to less than 1% among immunized children *(5)*. In 2020, WHO also released new guidelines on the use of peripartum prophylaxis with antivirals as an additional measure to prevent mother-to-child transmission of HBV.

This report focuses on progress in scaling up diagnosis and treatment for HCV. There is no vaccine available for hepatitis C, but there are effective prevention approaches. In addition to preventing new infections through blood and injection safety and harm reduction measures, global efforts to combat hepatitis C are based on reducing morbidity and mortality due to chronic liver disease through the delivery of diagnosis and treatment of HCV with highly effective antiviral agents, which are the focus of this report.

II Overview of the global hepatitis C epidemic and response

A high-burden disease with major opportunities to accelerate towards elimination

The global burden of HCV remains high. WHO estimates that 71 (62–79) million people worldwide were living with chronic HCV infection and 1.75 (1.57–2.12) million people were newly infected with hepatitis C virus in 2015. This resulted in at least 400 000 deaths each year, primarily due to liver cancer and cirrhosis caused by untreated HCV infections *(1)*.

HCV is prevalent worldwide. Low- and middle-income countries account for about 75% of people living with HCV. As shown in Table 1, the WHO Eastern Mediterranean Region and the WHO European Region have the highest estimated prevalence of HCV. There are large variations across countries. Four countries – China, Egypt, India and Pakistan – account for almost 40% of people living with HCV worldwide *(1)*. Unsafe health-care practices and injection drug use are among the leading modes of transmission of HCV. In many high- and middle-income settings, such as in North America and western and eastern Europe, most transmission is linked to former or current injecting drug use. Unsafe health-care practices (including unsafe health-care injections) contribute significantly to new infections in many low- and middle-income countries. In the Eastern Mediterranean Region, which has the highest rates of infection worldwide, the most common cause of transmission is unsafe health-care injections *(1)*.

People who inject drugs (PWID) are disproportionately affected by the HCV epidemic. A systematic review of the prevalence of injecting drug use among people aged 15–64 years found that in most regions and countries, 52.3% (42.4–62.1%) of PWID were infected with HCV (Table 2) *(6)*. A modelling study estimated that approximately 43% (25–67%) of new hepatitis C infections may be prevented over the period 2018–2030 if the increased risk for HCV transmission among PWID was removed *(7)*.

HCV also causes an additional burden through comorbidities. More than half of the HIV/HCV coinfections are estimated to be among PWID. A global systematic review and meta-analysis of the burden of HCV coinfection in people living with HIV (Table 2) found a consistently higher HCV prevalence in HIV-positive individuals than HIV-negative individuals across all risk groups and regions, but especially in PWID *(8)*. Another population group that is disproportionately affected includes men who have sex with men (MSM). A global systematic review of HCV prevalence and incidence in MSM found that HIV-positive MSM are at substantially higher risk of HCV; and for both HIV-negative and HIV-positive MSM, the pooled HCV prevalence was highest in low- and lower-middle-income economies *(9)*. However, there is a lack of disaggregated data overall on access to diagnosis and treatment services for these population groups, and more efforts are needed to build the evidence base and develop targets to ensure accountability for progress in these populations.

Table 1: Hepatitis C epidemic and response by WHO region, 2015

WHO region	Estimated prevalence of HCV infection (%), 2015	Estimated incidence of HCV infection per 100 000 population, 2015	Proportion of people infected who are diagnosed (%), 2015	Proportion of diagnosed people who are treated (%), 2015
African Region	1.0	31.0 [22.5–54.4]	5.7 [3.9–7.0]	2.2 [0.6–3.0]
Region of the Americas	0.7	6.4 [5.9–7.0]	36.3 [33.8–37.4]	11.1 [10.7–11.8]
South-East Asia Region	0.5	14.8 [12.5–26.9]	8.7 [6.0–9.8]	7.1 [4.9–8.4]
European Region	1.5	61.8 [50.3–66.0]	31.2 [25.2–34.7]	4.9 [4.2–7.2]
Eastern Mediterranean Region	2.3	62.5 [55.6–65.2]	17.7 [17.4–18.0]	12.1 [11.2–12.4]
Western Pacific Region	0.7	6.0 [5.6–6.6]	21.5 [20.3–21.6]	4.8 [4.7–5.0]

Source: Progress report on HIV, viral hepatitis and sexually transmitted infections, WHO 2019 and Global hepatitis report, WHO 2017.

Table 2: Regional and global estimates of people who inject drugs who are HIV-positive and anti-HCV positive, 2017

	HIV		HCV	
	Prevalence among PWID (95% uncertainty interval [UI])	**Estimated number of PWID living with HIV (95% UI)**	**Prevalence among PWID (95% UI)**	**Estimated number of PWID who are HCV-antibody positive (95% UI)**
Eastern Europe	24·7% (15·6–33·9)	747 000 (313 500–1 331 500)	64·7% (56·6–72·9)	1 955 500 (927 000–3 171 000)
Western Europe	4·5% (3·2–6·0)	46 000 (24 500–73 000)	53·2% (48·4–57·9)	537 000 (339 500–777 000)
East and southeast Asia	15·2% (9·9–20·4)	605 000 (375 000–879 500)	50·3% (37·7–62·8)	2 007 500 (1 337 500–2 783 500)
South Asia	19·4% (15·0–23·8)	198 500 (141 500–264 500)	38·6% (17·2–62·4)	395 000 (239 500–573 500)
Central Asia	10·5% (8·6–12·5)	29 500 (17 500–44 000)	54·0% (49·4–58·4)	152 000 (93 000–218 000)
Caribbean	13·5% (8·3–19·1)	11 000 (6000–16 500)	63·6% (54·3–72·6)	50 500 (31 000–73 000)
Latin America	35·7% (15·0–56·6)	651 000 (417 000–926 000)	61·9% (58·9–64·9)	1 128 000 (823 500–1 458 000)
North America	9·0% (7·0–11·1)	230 500 (105 000–389 000)	55·2% (40·8–67·7)	1 411 000 (667 000–2 388 500)
Pacific Island States and Territories*	16·3% (10·0–22·7)	3 500 (2000–5500)	55·5% (43·8–67·0)	12 500 (7500–18 000)
Australasia	1·1% (0·8–1·4)	1 000 (1000–2000)	57·1% (52·7–61·5)	66 000 (47 500–86 000)
sub-Saharan Africa	18·3% (11·3–25·4)	251 500 (75 000–508 500)	21·8% (17·6–26·5)	300 000 (90 500–608 000)
Middle East and North Africa	3·6% (1·5–6·2)	12 500 (4500–24 500)	48·1% (39·2–57·1)	168 000 (88 000–263 500)
Global	17·8% (10·8–24·8)	2 787 000 (1 482 500–4 464 000)	52·3% (42·4–62·1)	8 182 500 (4 691 500–12 418 000)

Source: Degenhardt et al. 2017 *(6)*.
**Note:* No estimates of the prevalence of HCV and anti-HCV could be located for the Pacific Island States and Territories, so the weighted observed global prevalence was used. Caution should be used in the interpretation of these estimates. The regional classification in this table is drawn from the original source and hence differs from the WHO regions.

Service coverage is increasing globally yet slowly, driven by large increases in a few countries

Access to the diagnosis and treatment of hepatitis is increasing in many countries, but progress is fragmented and global coverage remains low. The latest available global data indicate that, at the end of 2017, about 20% of the 71 (62–79) million people living with chronic HCV infection in low- and middle-income countries knew their status, as compared to less than 5% at the end of 2015. Worldwide, about 5 million people chronically infected with HCV were cumulatively receiving treatment at the end of 2017; a fivefold increase from 1 million people receiving treatment at the end of 2015 *(10)*, but representing a coverage of only 7%. Updated data will be available in 2021.

Among the 12 countries highlighted in this report, comparable yearly data on access to hepatitis C treatment are available from eight countries. In these countries, the cumulative number of people receiving hepatitis C treatment grew more than 20-fold between 2015 and 2018 – from about 122 000 patients at the end of 2015 to more than 2.6 million by the end of 2018. A few countries such as Brazil, Egypt and Pakistan account for a large proportion of the global increase. Further details on country achievements are presented in Chapter III.

Updated global guidelines provide an opportunity for widespread public health scale up

In 2016, WHO Member States endorsed three aligned global health sector strategies on HIV, viral hepatitis and sexually transmitted infections (STIs) to guide actions towards elimination of these diseases. The Global Health Sector Strategy on Viral Hepatitis 2016–2021, the first comprehensive global strategy for addressing viral hepatitis, aims to achieve a 90% reduction in the incidence of hepatitis B and C virus by 2030, and a 65% reduction in mortality in order to eliminate viral hepatitis as a major public health threat by 2030. This would require 90% of those infected to be diagnosed, and 80% of those diagnosed to be treated *(4)*.

The 2017 WHO guidelines on testing for hepatitis B and C reviewed the most accurate testing strategies for countries to follow *(11)*. The guidelines recommend one serological assay (rapid diagnostic test [RDT] used at the point of care [POC]/ laboratory, or immunoassay performed in the laboratory) to test for the presence of anti-HCV antibodies (a marker of past or current exposure to HCV); followed by detection of HCV RNA or HCV core antigen to diagnose chronic HCV infection.

Assessment of liver disease is done using non-invasive tests such aspartase aminotransferase-to-platelet ratio index (APRI) or transient elastography. The use of genotyping has decreased due to the advent of pangenotypical DAAs. HCV nucleic acid testing (NAT) is the preferred option for assessment of cure, and ultrasound and alpha-fetoprotein for monitoring of hepatocellular carcinoma among patients with advanced liver fibrosis, even after cure of HCV infection.

In 2018, WHO published updated guidelines for the screening, care and treatment of persons with chronic HCV infection (Box 3) *(12)*. These guidelines introduced major simplifications in the delivery of treatment services, adopting a "treat all" approach that recommends that all people living with chronic HCV infection (with the exception of pregnant women and children under 12 years) should start treatment immediately, irrespective of disease stage, with DAA drugs, which can cure more than 90% of chronic HCV cases. The guidelines also recommend the use of pangenotypic regimens, which can treat all strains of HCV, eliminating the need for more specialized genotyping to determine the drug regimen.

Box 3
Overview of the WHO treatment guidelines for adults and adolescents, 2018

Patients ≥18 years without cirrhosis	• Glecaprevir/pibrentasvir 8 weeks* • Sofosbuvir/daclatasvir 12 weeks • Sofosbuvir/velpatasvir 12 weeks (pangenotypic regimens)
Patients ≥18 years with compensated cirrhosis	• Glecaprevir/pibrentasvir 12 weeks* • Sofosbuvir/daclatasvir 24 weeks • Sofosbuvir/daclatasvir 12 weeks** • Sofosbuvir/velpatasvir 12 weeks (pangenotypic regimens)
Adolescents 12–17 years* **	• Sofosbuvir/ledipasvir 12 weeks in genotypes 1, 4, 5 and 6 • Sofosbuvir/ribavirin 12 weeks in genotype 2 • Sofosbuvir/ribavirin 24 weeks in genotype 3 (genotype-dependent regimens)

* Persons with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.
** May be considered in countries where genotype distribution is known and genotype 3 prevalence is <5%.
*** Treatment in adolescents at this time still requires genotyping to identify the appropriate regimen.
Source: Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection, WHO; 2018.

In addition, the updated guidelines provide eight key good practice principles to support simplified service delivery across the continuum of care:

i. comprehensive national planning for the elimination of HCV infection based on the local epidemiological context, existing health-care infrastructure, current coverage of testing, treatment and prevention, and available financial or human resources;

ii. simple and standardized algorithms across the continuum of care from testing, linkage to care and treatment;

iii. strategies to strengthen linkage from testing to care, treatment and prevention;

iv. integration of hepatitis testing (screening and diagnosis), care and treatment with other services (e.g. HIV services) to increase the efficiency and reach of hepatitis services;

v. decentralized testing (screening and diagnosis) and treatment services at primary health facilities or harm reduction sites to promote access to care – through task-sharing, supported by training and mentoring of health-care workers and peer workers. This can also be done through a differentiated care strategy to assess level-of-care needs, with specialist referral, as appropriate, for those with complex problems;

vi. community engagement and peer support to promote access to services and linkage to the continuum of care, which includes addressing stigma and discrimination;

vii. strategies for more efficient procurement and supply management of quality-assured, affordable medicines and diagnostics;

viii. data systems to monitor the quality of individual care and coverage at key steps along the continuum or cascade of care at the population level.

In 2019, WHO also published consolidated strategic information guidelines for viral hepatitis, which summarize and simplify the overall approach proposed by WHO to collect, analyse, disseminate and use strategic information on the cascade of the viral hepatitis response at local, subnational, national and international levels in order to assess gaps and ensure data-driven decision-making *(13)*.

The Global Health Sector Strategy and the related guidelines, together with strong national commitment, enhanced access to hepatitis C diagnosis and pharmaceutical products, and improved quality standards and regulation, offer an opportunity to rapidly accelerate a public health response to HCV. Further details on the key enablers of scale up are described in Chapters III and IV.

More countries have national strategic plans, but efforts are needed to make these more robust

The adoption of the Global Health Sector Strategy on Viral Hepatitis 2016–2021 provided a vital impetus for countries to develop or update their national strategic plans for viral hepatitis and integrate the response into broader efforts to achieve universal health coverage. While less than 20 countries had national viral hepatitis strategic plans in 2012, this had increased to 124 countries by 2018 *(14)*.

Further efforts are needed to make these plans more robust, simple and ambitious, including in high-burden priority countries. For example, in 2018, a WHO desk review of national strategic plans for HIV, STIs, tuberculosis (TB), viral hepatitis and the health sector in 55 countries found that less than half had clear impact targets to reduce the morbidity and mortality from viral hepatitis, and did not include efforts to strengthen strategic information on viral hepatitis. The majority did not include commitments to increase domestic financing for the response.[a]

Another desk review in 2019 specifically assessed the landscape of country hepatitis policies for harm reduction and hepatitis C testing and treatment for PWID and people in prisons in 81 of the 124 countries with national strategic plans for viral hepatitis as of 2018 *(Fig. 1)*. Of these 81 plans, less than half outlined the necessary interventions for PWID in accordance with the Global Health Sector Strategy on Viral Hepatitis. As many as 30 plans did not reference PWID as a target population group for interventions at all. Interventions for people in prisons were similarly lacking – only 28 plans referenced interventions for this population group *(14)*.

Some countries are adopting targeted micro-elimination approaches to accelerate progress

Micro-elimination approaches break down national elimination goals into smaller goals for individual population or geographical segments, for whom treatment and prevention interventions can be delivered more quickly and effectively using targeted methods. The scope of these approaches varies and can include micro-elimination in a specific population nationally, or on a smaller geographical scale such as regionally or at a city level *(15)*.

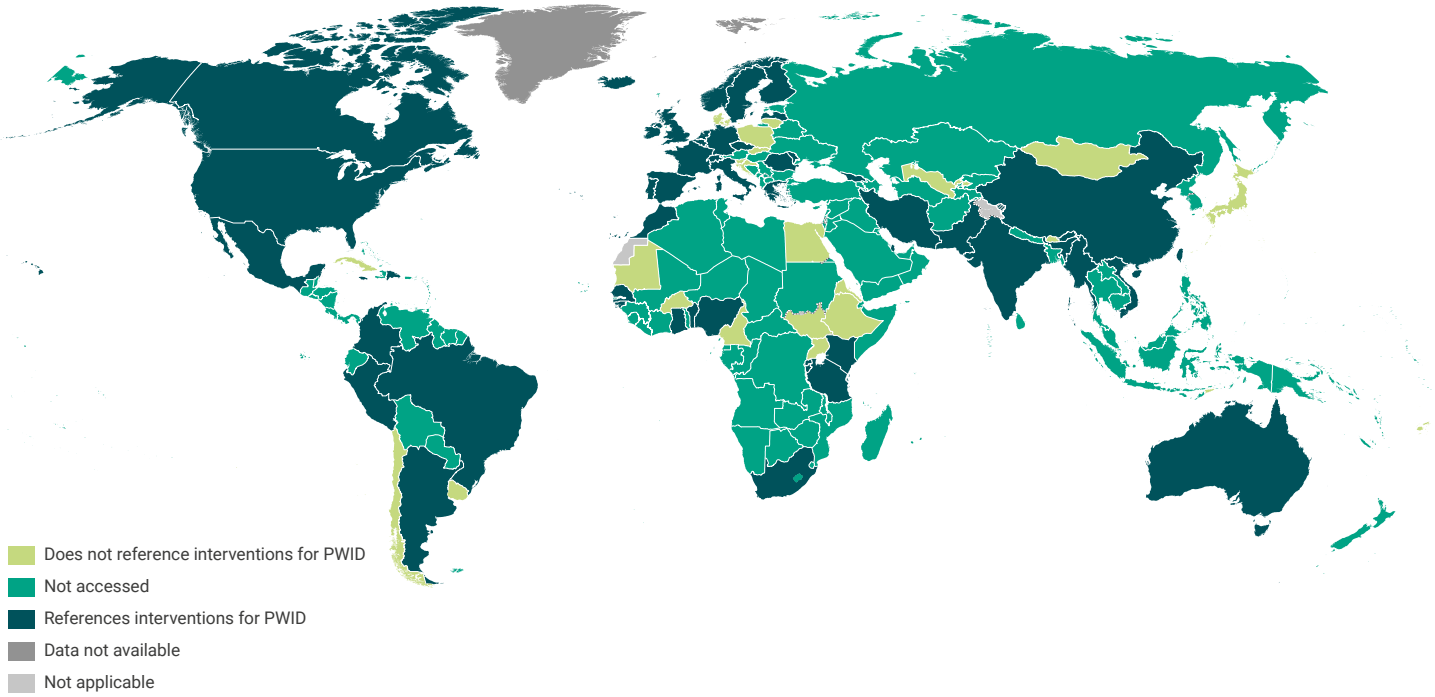
A number of countries are piloting such approaches in different settings as a pragmatic and efficient strategy to accelerate progress towards national elimination goals. The Netherlands is pursuing multiple micro-elimination initiatives within the country among subpopulations with an increased and/or a high prevalence of HCV, including migrants from high-endemic countries, PWID, people in prisons, MSM, people living with HIV, patients with haemophilia, patients on haemodialysis and health-care workers. The micro-elimination approach is implemented in collaboration with several institutions involved in public health-care delivery in the country and includes dedicated information campaigns, screening and diagnosis among identified groups, and linkage to care in dedicated services. A study modelling the future HCV burden of disease in the Netherlands estimated an 85% reduction in chronic HCV infections by the year 2030, if treatment and prevention can be scaled up adequately *(16)*.

In Canada, a mathematical model estimated that prison-based test-and-treat strategies could lead to a 48% decline in the incidence of HCV over 2018–2020, and prevent the largest number of new infections among people never exposed to HCV. When implemented along with other community-based interventions to reduce post-release transmission risk, the prison-based interventions had synergistic effects, averting a larger number of new infections *(17)*.

Other countries are pursuing micro-elimination approaches in a defined geographical area as a path towards national elimination. For example, Egypt implemented a comprehensive community-based "educate, test and treat" programme in 73 villages across seven governates as a model for the elimination of HCV infection in rural communities. Between June 2015 and June 2018, 204 749 (92.3%) of 221 855 eligible villagers aged 12–80 years were screened for HCV antibody. Of these, 33 839 (16.5%) were positive, giving a 7.8% prevalence of HCV viraemia.

a Desk review of national HIV, STI, tuberculosis, viral hepatitis and national health strategies in WHO priority HIV and hepatitis countries to determine the level of programme and service integration and linkages described in the strategies/plans. Geneva, WHO 2018 (unpublished).

Fig. 1: National plans and/or treatment guidelines referencing interventions for hepatitis C virus in people who inject drugs



Source: https://apps.who.int/iris/bitstream/handle/10665/312116/WHO-CDS-HIV-19.6-eng.pdf?ua=1

Overall, treatment coverage and cure were achieved in around 85% of the infected adults, and in the subsequent two years, there was a substantial reduction in the incidence of new HCV infections in nine of the villages re-examined *(18)*. The simplified public health approach with strong community education and engagement resulted in low rates of loss to follow up and good treatment outcomes *(19)*. A similar community-based micro-elimination model is being implemented across Punjab province in Pakistan, where a significant proportion of the HCV-infected population live in rural areas *(20)*.

Some countries are also leveraging their HIV response to target micro-elimination of HCV among people living with HIV. For example, Cambodia is screening HIV-positive patients for HCV by leveraging the existing HIV laboratory infrastructure to reduce the costs of diagnosis and sample transportation, and is providing HCV treatment to people living with HIV with financial support from The Global Fund to Fight AIDS, TB and Malaria (Global Fund).

Intercountry and interregional collaboration are important for sharing experiences and lessons learned

As countries strive to reach the goal of elimination, many are gathering diverse and valuable experiences that address their specific challenges in terms of policy, planning, service delivery, market dynamics, financing and meeting the needs of the most vulnerable. Some of these experiences are highlighted in Chapters III and IV. It is critical that global efforts continue to foster south–south cooperation so that countries can share such knowledge and lessons learned from different contexts (Box 4).

Box 4
South–South learning: Egypt's support to countries in the African Region

In 2019, Egypt – which has had one of the world's largest hepatitis C epidemics – announced that it would be supporting hepatitis C testing and treatment for 1 million people primarily in 14 African countries that bear a high hepatitis burden: Burundi, Chad, the Democratic Republic of Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Kenya, Mali, Somalia, South Sudan, Sudan, Tanzania and Uganda. In 2020, this was further expanded to 18 countries – Burkina Faso, Burundi, Chad, the Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Guinea Bissau, Kenya, Mali, Nigeria, Rwanda, Somalia, South Sudan, Sudan, Tanzania and Uganda. Egypt's support to the African continent has also included the provision of technical expertise and tools, and will be delivered in collaboration with WHO *(21)*. Since mid-2019, Egypt has already provided support to Chad, Eritrea and South Sudan. A total of 36 183 individuals have been screened for HCV infection with Egyptian support, and 649 patients have started treatment with DAAs.

III Progress in 12 selected countries

This section highlights the progress achieved in 12 low- and middle-income countries with diverse hepatitis C epidemics and national responses: Brazil, China, Egypt, Georgia, India, Malaysia, Mongolia, Morocco, Pakistan, Russian Federation, Rwanda, Ukraine. Of these, four countries – China, Pakistan, India and Egypt – account for about 40% of all people living with HCV worldwide.

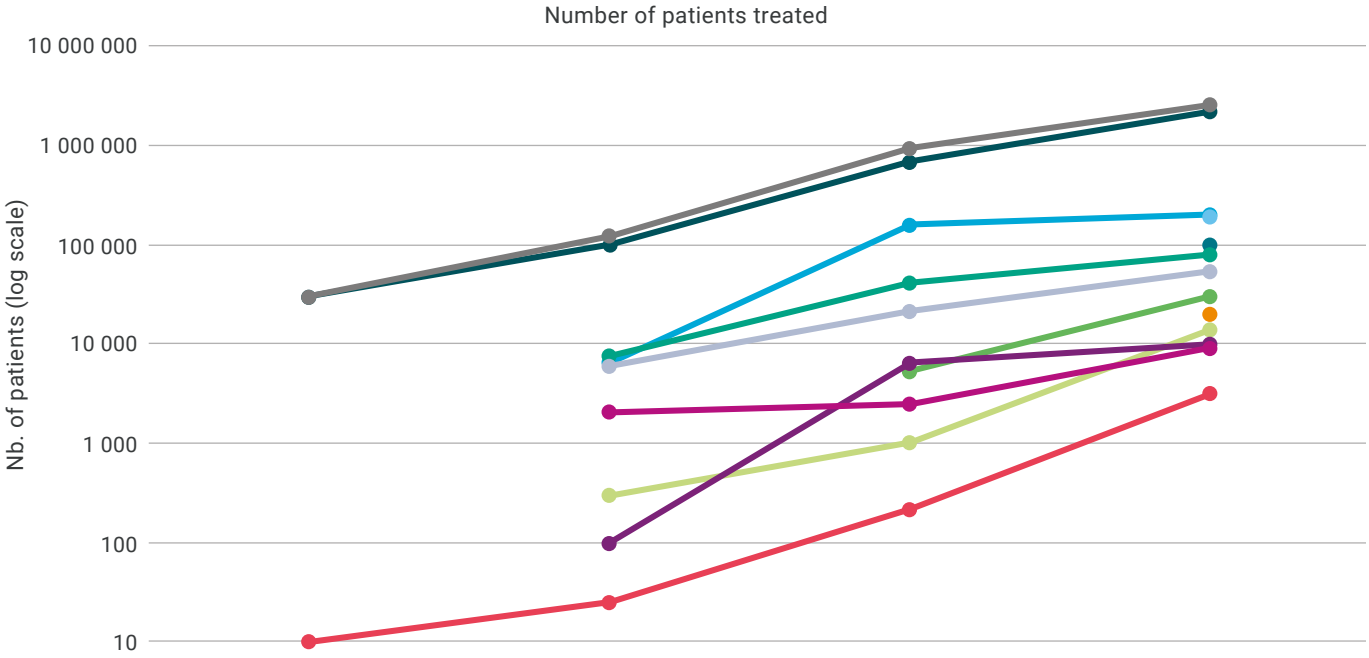
Together, these 12 countries represent a diverse range of country contexts and experiences in their HCV response, and are adopting various strategies to enhance access to hepatitis C services. They were selected to highlight their successful approaches and recent achievements in relation to the main building blocks of successful programmes – including developing national plans, providing an efficient regulatory environment and quality assurance of products, addressing pricing and patent-related barriers, and focusing on the needs of the most vulnerable. Their efforts to address ongoing barriers also provide valuable inputs to other low- and middle-income countries as they scale up their programmes.

Uptake of direct-acting antivirals is increasing steadily, but at an uneven pace

All 12 countries demonstrate a steady increase in the number of patients with chronic HCV infection who are receiving treatment with DAAs. Among the eight countries with previous comparable data points (Brazil, Egypt, Georgia, Malaysia, Mongolia, Morocco, Rwanda and Ukraine), the total cumulative number of patients treated increased more than 20-fold between 2015 and 2018 – from a low baseline of about 122 000 patients at the end of 2015 to more than 2.6 million by the end of 2018 *(Fig. 2)*.

The largest increase was observed in Egypt, where more than 1.5 million additional people started treatment through a nationwide campaign in 2018. The total cumulative number of people on treatment increased from 30 000 in 2014 to more than 2 million patients by mid-2019. Other countries also saw large increases since 2015, for example, from nearly 6000 patients in 2015 to more than 53 000 patients in 2018 in Georgia, from 300 patients in 2015 to 13 800 patients in 2018 Rwanda, and from no patients in 2015 to 30 000 patients in 2018 in Mongolia.

Fig. 2: Cumulative number of people receiving hepatitis C treatment in 12 selected countries – 2014–2018*



	2014	2015	2016	2018
Egypt	30 000	100 000	700 000	2 236 670
Pakistan	0	6 500	161 000	200 000
China				200 000
India				100 000
Brazil	0	7 459	41 226	78 666
Georgia	0	5 941	21 654	53 393
Mongolia	0	0	5 294	30 000
Russian Federation				20 000
Rwanda	0	300	1 000	13 800
Morocco	0	100	6 500	10 000
Ukraine	0	2 000	2 500	9 295
Malaysia	10	25	220	1 537
TOTAL	30 010	122 325	939 519	2 604 599

Data source: Report of the WHO survey on access to DAAs, 2019 (*Note:* India – unconfirmed reports)
* Data were not collected for 2017.

Coverage of testing services also shows progress, but remains low

The coverage of HCV testing and diagnostic services is also increasing, but the majority of people living with HCV remain undiagnosed. The WHO 2017 *Guidelines on hepatitis B and C testing,* and the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection,* recommend a simplified two-step testing strategy to diagnose chronic HCV, with a single laboratory-based test or RDT for the detection of antibodies to HCV (for screening) followed immediately by testing for the detection of HCV RNA or HCV core antigen to confirm viraemic infection that would benefit from treatment. One last HCV RNA test is recommended for assessment of cure. This simplified approach, together with the use of pangenotypic regimens that remove the need for genotyping, offer a crucial opportunity to scale up testing and diagnosis across a wide range of clinical setting *(12)*.

Countries are adopting public health approaches to accelerate scale up

Access strategies for many low- and middle-income countries are based on generic competition. Most low- and middle-income countries are included in voluntary licenses of originator companies Gilead, BMS and AbbVie (either directly or through the Medicines Patent Pool [MPP]), which give them access to generic DAAs and the opportunity to further reduce prices through generic competition. Additional countries have gained access following the decision by BMS that the market authorizations and patents for its product daclatasvir would be withdrawn or allowed to lapse (further details in Section IV.3) *(22)*. Some countries, including Georgia, India and Malaysia, have also been beneficiaries of a grant from Unitaid to support access to HCV testing and treatment *(23)*.

The 12 countries highlighted in this report are already demonstrating how progress can be accelerated through a public health approach, with committed political leadership, strong national planning and approaches to leverage price reductions of diagnostics and treatment. Table 3 highlights some of the key elements of the national responses in these countries. Although each country context is unique, the examples highlight how they are successfully adopting the common elements of a public health approach, including WHO recommendations for simplified diagnostics, optimized treatment protocols, decentralized delivery, and promotion of equity, in relation to their local needs and realities.

Brazil. Brazil has a large HCV burden, with an estimated 1.1 million infections in 2017 *(24)*. DAAs have been available in Brazil since 2014. Testing and treatment are provided free of charge in the public sector for all HCV-infected patients, and there has been an expansion of screening services to the primary health-care level. Brazil updated its treatment guidelines in 2018 to expand treatment eligibility regardless of stage of disease. In 2015, less than 8000 people were receiving treatment. By the end of 2018, Brazil had achieved a large expansion in its screening programme and treated 78 666 patients, a significant step towards to meeting its national targets yet still a long way from universal access. The DAAs available in the country include sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir. Brazil can import only originator products as it is currently not included in voluntary licensing agreements. The Ministry of Health (MoH) has opened a bidding process for all products included in the national guidelines. The lowest prices obtained with Gilead include sofosbuvir/ledipasvir at US$ 1148 and sofosbuvir/velpatasvir at US$ 1470 per treatment course. Glecaprevir/pibrentasvir is available at US$ 4865 per treatment course. Brazil is also expanding efforts to enable local production of generic versions of sofosbuvir and daclatasvir *(25)*. Ongoing challenges for the national programme include the continued high cost of pangenotypic treatment, availability of treatment only by generalist doctors at primary health-care levels, how to further expand nurse-led screening, and increase access in remote areas.

China. With an estimated 7.6 million HCV infections at the start of 2016, China faces among the largest burdens of HCV worldwide.[b] The first DAAs became available in China in 2015, followed by the development of a new National Plan for the Prevention and Control of Viral Hepatitis (2017–2020).[c] The Plan includes standardization of testing and treatment, improved registration of DAAs to ensure timely supply, price reductions through centralized negotiations with manufacturers, and the use of compulsory licensing where necessary. The treatment guidelines were updated in 2019, and China plans to update its National Plan for the next five-year period. A number of DAAs and combinations, both imported from international companies and developed locally, are available in the country. Some DAAs are covered by provincial or local health insurance schemes, yet the prices remain very high at about US$ 9 000 for a 3-month course and overall population-wide access is limited due to patent-related barriers. In 2016, only 125 000 of the estimated 7.6 million patients with chronic HCV were receiving treatment in China, which increased to around 200 000 by mid-2017. In 2019, national price negotiations for hepatitis C medicines led by the national health insurance agency resulted in an 85% reduction of the retail prices of several DAAs, including pangenotypic regimens. This price reduction allowed the inclusion of three DAA combinations (sofosbuvir/ledipasvir, sofosbuvir/velpatasvir and elbasvir/grazoprevir) under the national health insurance scheme from January 2020, facilitating an expansion in access to treatment. A pilot programme in Shanghai is also exploring the combined delivery of hepatitis prevention, treatment and care with the existing chronic disease management system to test and develop a path towards universal access.

b National estimates, obtained through WHO Regional Office for the Western Pacific.
c Landscape on access to medicines for the continuum of hepatitis B and C treatment in the Western Pacific Region: country report China. 2019 (internal document).

Table 3: Key elements of national access strategies in 12 selected countries, 2019

Country name	Last update of HCV treatment guidelines (year)	HCV testing and treatment available free of charge in the public sector (Y/N)	Product registration	Inclusion in licensing agreements for DAAs: • Gilead licensing agreement for SOF, SOF/LDV, SOF/VEL • BMS and MPP licensing agreement, or patent withdrawal/lapse for DCV • AbbVie and MPP licensing agreement for G/P	Generic local production	Highlights of recent strategies to expand access to HCV services
Brazil	2018	Yes	Originators and generics	None	No (planned)	Price negotiations, patent oppositions
China	2019	Yes, as part of health insurance	Originators only	None	Yes (local production of other DAAs)	Price negotiations, integration with health insurance schemes
Egypt	2019	Yes	Originators and generics	SOF SOF/LDV SOF/VEL DCV G/P	Yes	Nationwide screening and treatment campaign, local production
Georgia	2018	Yes	Originators only	DCV G/P	No	Integration with harm reduction, civil society role
India	2018	Yes	Generics only	SOF SOF/LDV SOF/VEL DCV	Yes	Local production
Malaysia	2017	Yes	Originators and generics	SOF SOF/LDV SOF/VEL DCV	No	Compulsory license, price negotiations, nationwide screening and treatment campaigns
Mongolia		Yes, as part of health insurance	Originators and generics	SOF SOF/LDV SOF/VEL DCV	No	Nationwide screening and treatment, health insurance schemes
Morocco	2018	Yes	Originators and generics	SOF SOF/LDV SOF/VEL DCV G/P	Yes	Price negotiations to launch national treatment programme, local production
Pakistan	2019	Yes	Generics only	SOF SOF/LDV SOF/VEL DCV G/P	Yes	Coordination of provincial programmes, local production of DAAs, high-level government initiative for HCV elimination
Russian Federation		Yes	Originators only	None	No	Price negotiations, health insurance schemes
Rwanda	2019	Yes	Originators and generics	SOF SOF/LDV SOF/VEL DCV G/P	No	Task-shifting, price negotiations
Ukraine		Yes	Originators and generics	SOF SOF/LDV SOF/VEL DCV	No	Price negotiations, civil society role

Data source: Report of the WHO survey on access to DAAs, 2019 and Medicines Patent Pool *(22)*.
DCV: daclatasvir; LDV: ledipasvir; G/P: glecaprevir/pibrentasvir; SOF: sofosbuvir; VEL: velpatasvir.

Egypt. Faced with one of the world's largest HCV epidemics, Egypt has made major progress in its response to HCV since 2014 through a public health approach backed by strong government commitment, local generic manufacturing, major price reductions through negotiations with manufacturers, and large expansion in testing and service delivery. At the start of 2016, Egypt had about 5.6 million HCV infections *(26)*. In 2018, Egypt launched a massive countrywide effort to screen the entire population aged 18 years and older (a target population of 62.5 million people) within one year and provide treatment paid for by the State to all those with infection. Nearly 50 million adults and 9 million children aged 12–18 years were screened by mid-2019 *(27)*. The overall HCV seroprevalence was found to be 4.61%, with regional variations. More than 1.5 million additional people, or nearly 92% of those confirmed to be viraemic through the screening programme, had started treatment by mid-2019, bringing the total number of people on treatment to more than 2 million. The screening programme will continue with a focus on high-risk groups, including people with HCV/HIV coinfection, hospitalized patients and people in prisons, along with a mass communication programme to raise awareness.
The national treatment protocols include sofosbuvir/daclatasvir, among others. Egypt has made major progress in bringing down the prices of HCV treatment, and is expanding harm reduction for PWID. A locally produced fixed-dose combination of sofosbuvir/daclatasvir is now available at US$ 16 per 28-day supply, or less than US$ 50 for a 12-week treatment course. In 2017, this was available only as stand-alone sofosbuvir and daclatasvir at US$ 60 per 28-day supply for both. The approach shows the feasibility of universal access based on rapid, widespread testing and affordable treatment.

Georgia. A national cross-sectional seroprevalence survey conducted in 2015 estimated that around 150 340 people aged 18 years and older in Georgia are living with chronic HCV infection *(28)*. The national strategic plan for the elimination of hepatitis C virus in Georgia aims to treat all persons chronically infected with HCV through decentralized service delivery, including testing and treatment at primary health-care services and harm reduction centres. Georgia was the first country in the WHO European Region to set targets for the elimination of HCV by 2020 *(29)*. Treatment guidelines were updated in 2018. All HCV diagnostics, including for pre-treatment and treatment monitoring, are provided free of charge. To improve case-finding among the general population, an innovative approach of integrated screening for HCV, HIV and TB by primary health-care providers was implemented in the Samegrelo-Zemo Svaneti Region in 2018 and further expanded to six more regions in 2019 *(30)*. The cumulative number of patients who had received treatment increased tenfold, from about 6000 in 2015 to 21 000 in 2016 to over 60 000 by mid-2019. Approximately one third of the patients are in the capital Tbilisi. The DAAs available in the country are sofosbuvir, sofosbuvir/ledipasvir and, since December 2018, sofosbuvir/velpatasvir, which is provided by Gilead as a donation with the framework of an agreement signed in 2015. Support from Gilead towards the national goal of elimination is expected to continue. Georgia is also part of a Unitaid-funded initiative to expand access to HCV diagnostics and demonstrate the integration of HCV testing into HIV programmes. It is supported by the Foundation for Innovative New Diagnostics (FIND), in collaboration with national authorities and the Georgian Harm Reduction Network. Some of the main challenges to achieving elimination targets relate to the marginalized status of PWID and barriers faced by them in accessing services, including continuous criminalization of drug use, difficulties with identifying people in need of treatment, and high rates of loss to follow up.

India. With more than 6 million estimated HCV infections at the start of 2016, India also faces a large HCV burden *(26)*. The national viral hepatitis control programme of the MoH aims to achieve elimination of viral hepatitis as a public health threat by 2030. Treatment guidelines were last updated in 2018 and regimens include sofosbuvir/daclatasvir and sofosbuvir/velpatasvir. HCV treatment is provided free of charge in the public sector and is being rolled out across the country. Nearly 100 000 people (unconfirmed) were receiving HCV treatment in India by 2019, a low coverage in relation to the estimated need of more than 6 million people. Further, coverage varies across states. The lowest price of generic sofosbuvir + daclatasvir reported in India for the domestic market was around US$ 39 per treatment course *(31)*. India is also part of a Unitaid-funded initiative supported by FIND in the states of Delhi, Manipur and Punjab, in collaboration with the relevant state and national authorities, the Institute of Liver and Biliary Sciences and the YR Gaitonde Centre for AIDS Research and Education (YRG CARE), to expand access to HCV diagnostics and demonstrate the integration of HCV testing into HIV programmes. Greater involvement of civil society organizations and patient groups, especially those representing vulnerable populations, will be needed to achieve universal access goals.

Malaysia. At the start of 2016, there were an estimated 382 000 HCV infections in Malaysia *(26)*. HCV treatment became available in Malaysia in 2018, following government negotiations on price reductions with innovator companies. A total of 1537 hepatitis C patients had received treatment until the end of 2018, increasing to 5849 patients by the end of 2019.[d] Malaysia was the first country to issue a government-use or compulsory license to enable local companies to manufacture sofosbuvir or import generic sofosbuvir into the country under certain conditions. Community-based organizations played an important role in advocating for and supporting the government's decision to accelerate access to low-cost treatment. Subsequently, Gilead also included Malaysia in their voluntary licensing territory. Following these negotiations, Malaysia launched the provision of free HCV treatment with DAAs in 11 government hospitals in 2018 and has since expanded treatment nationwide with decentralization of services to primary care facilities. Sofosbuvir, available as originator product for US$ 11 200 per treatment course, is available for less than US$ 100 per treatment course as of mid-2020 from a generic supplier. The national treatment guidelines were updated in 2017. Malaysia now offers free universal treatment with sofosbuvir + daclatasvir. Several generic DAAs are now registered in the country and are imported from generic Indian and Egyptian suppliers. The overall cost of sofosbuvir + daclatasvir ranges between US$ 225 and US$ 291 per treatment course. Malaysia is also part of a Unitaid-funded initiative supported by FIND and the Drugs for Neglected Diseases *initiative* (DND*i*) to decentralize screening for HCV using pre-qualified RDTs and link people in need to treatment services.

d Chan H-K, Hassali MA, Said RM, Abu Hassan MR. Treatment coverage and drug expenditure in hepatitis C patients from 2013 to 2019: a journey of improving treatment availability in Malaysia through government-led initiatives. Hepat Mon. 2020;20(9):e107372. doi:10.5812/hepatmon.107372.

Mongolia. Mongolia had an estimated 194 000 HCV infections at the start of 2016 *(26)*. Backed by strong political leadership, Mongolia is the first lower-middle-income country in Asia and the Pacific to commit to hepatitis elimination by ensuring universal health insurance coverage for hepatitis testing and treatment for its entire population *(32)*. Mongolia's national Healthy Liver Program, launched in 2017 to target the 40–65 years age group, reached more than 350 000 people with screening within its first year of implementation. About 22 500 patients with hepatitis C were diagnosed through this effort, and more than 80% were treated with DAAs. The main DAA in use is sofosbuvir/ledipasvir appropriate to the genotype, available at around US$ 230–240 per 3-month course, including for ERP-reviewed products, which is around the threshold reimbursement level of health insurance. Sofosbuvir/daclatasvir costs more than US$ 240, as daclatasvir is imported in small quantities for people who fail sofosbuvir/ledipasvir. As Mongolia continues to accelerate screening and treatment, prices remain a challenge. Mongolia continues to pay prices higher than other countries in the region, as a result of several factors, including high import taxes, the small size of the market, and the lack of pooled procurement options.

Morocco. There were an estimated 263 000 HCV infections in Morocco at the start of 2016 *(26)*. Access to DAAs is increasing progressively. The country has committed to a national plan for the elimination of HCV infection, and updated its national treatment protocols to include sofosbuvir/daclatasvir, sofosbuvir/velpatasvir and sofosbuvir/ribavirin. Of these, daclatasvir, sofosbuvir and sofosbuvir/daclatasvir are locally produced. In addition, sofosbuvir/ledipasvir is imported from originator and generic manufacturers, and sofosbuvir/velpatasvir from originators. All medicines are available in the private sector; however, DAAs are currently not available in the public sector. About 10 000 patients have received treatment to date in the private sector, at a price of around US$ 150 per 28-day supply of daclatasvir and around a US$ 300 per 28-day supply of sofosbuvir. The prices of a fixed-dose combination of sofosbuvir/daclatasvir, which received recent market authorization is US$ 330 per 28-day supply or US$ 990 per treatment course. In 2019, the Government of Morocco finalized the purchase of diagnostic tests to begin providing testing free of charge to all patients, with plans to start a national treatment programme at the end of 2019 in five national referral hospitals, 70 provincial hospitals and 12 district hospitals. The main challenges faced by the programme include the lengthy process for obtaining marketing authorization and high prices, leading to delays in making DAAs available in the public sector; and the lack of universal coverage of social security schemes. Civil society organizations are supporting the delivery of services to key populations.

Pakistan. With more than 10 million estimated HCV infections at the start of 2020, Pakistan faces among the largest HCV burdens worldwide.[e] On World AIDS Day 2019, the Federal Government announced a new programme – the Prime Minister's Programme for the Elimination of HCV Infection in Pakistan – by 2030 *(33)*. The Programme is the first to provide leadership and coordination to provincial hepatitis programmes in scaling up access to hepatitis prevention, testing and treatment services, in collaboration with national efforts to promote injection safety, safe blood transfusion and infection control. Pakistan bears a heavy burden of hepatitis, with a low coverage of diagnosis and treatment services and a threefold increase in annual reported liver cancer cases. Pakistan is now providing HCV testing and treatment free of charge in the public sector. The programme is growing but is yet to reach scale. The number of people treated has increased from about 6500 in 2015 to 200 000 by the end of 2018, 40% of whom accessed treatment in the public sector, particularly in Punjab province. The national treatment guidelines include sofosbuvir/daclatasvir, sofosbuvir/velpatasvir and sofosbuvir/ribavirin. DAAs are produced locally. The reported price of a locally produced fixed-dose combination of sofosbuvir/daclatasvir is US$ 7 per pack in the public sector, or less than US$ 30 per treatment course. A study published by WHO shows that Pakistan would see a return on its investments in eliminating hepatitis within 3 years, as more people would access hepatitis testing and treatment sooner, reducing the costs of the long-term care required for liver cirrhosis and cancer *(34)*.

Russian Federation. With close to 5 million people estimated to be anti-HCV positive, the Russian Federation faces a major public health challenge to scaling up access to testing and treatment *(26)*. DAAs have been available in the Russian Federation since 2015 and HCV testing is provided free to all patients. In 2019, two pangenotypic DAA regimens were available in the Russian Federation – sofosbuvir + daclatasvir and glecaprevir/pibrentasvir. About 20 000 people were reported to be receiving treatment at the end of 2018, leaving a substantial gap in coverage. Funding for hepatitis C treatment programmes remains limited. One of the major challenges faced by the Russian Federation is the high prices of hepatitis C medicines due to high levels of patent protection and because the country is not included in the licensed territory by Gilead. The availability of generic DAAs is limited in the Russian Federation (daclatasvir is manufactured by a local generic manufacturer under exclusive license from the originator BMS) *(35)*. Access to DAAs in the public health-care system has been rationed and, although the Federal Antimonopoly Service (FAS) and civil society have made efforts to introduce compulsory licensing legislation, none have been issued to date *(36)*. The prices reported in 2019 were US$ 1188 per 28-day supply for daclatasvir from BMS, US$ 5071 per 28-day supply for glecaprevir/pibrentasvir from AbbVie and US$ 3338 per 28-day supply for sofosbuvir from Gilead. A recent report on DAA procurement by ITPCru showed that the price of sofosbuvir had decreased in 2019 to US$ 1834 and continued to decrease in 2020 to US$ 1099 per 28-day supply, yet price remains a significant barrier *(37)*.

Rwanda. At the start of 2016, Rwanda had an estimated 63 000 HCV infections *(26)*. Building on its successful public health response to improve HIV, TB, malaria and maternal and child health outcomes, Rwanda is now also investing resources to accelerate the response to viral hepatitis. The Rwandan government committed in 2018 to eliminate HCV by 2023. In 2019, the government publicly accelerated its target date for

e Information from the WHO Country Office, September 2020.

elimination to 2021. The key elements of Rwanda's national elimination plan include simplified treatment algorithms, selective partnerships and preferred suppliers to drive down prices. Other elements are finding operational efficiencies in service delivery through approaches such as task-shifting to nurses and decentralized screening with RDTs at the primary health-care level *(29)*. The national treatment protocols were updated in 2019 and include sofosbuvir/ledipasvir, sofosbuvir/daclatasvir and sofosbuvir/velpatasvir. Generic products are available and testing and treatment are provided free of charge. The lowest available market price for a WHO-prequalified treatment course with sofosbuvir and daclatasvir is US$ 60, the preferred DAA regimen in Rwanda, which is among the lowest available prices reported in low-income countries for a WHO-prequalified regimen *(31)*. With these efforts, Rwanda has substantially increased the number of patients receiving treatment, from about 300 in 2015 to nearly 14 000 in 2018 and 25 000 by mid-2020, the majority of whom are treated in the public sector.

Ukraine. Ukraine also faces a large HCV burden with an estimated 1.4 million chronic HCV infections at the start of 2016 *(26)*. There have been a number of recent developments in increasing access to HCV services in Ukraine. Civil society organizations such as Alliance for Public Health Ukraine (APH) have played a key role in advocacy to develop and adapt national policies according to WHO recommendations, and provide service delivery. Updates to the national plan for elimination of viral hepatitis and national treatment guidelines for HCV are under way, and international guidelines, including from WHO and the European Association for the Study of the Liver (EASL) are in use in the meantime. The DAAs available within the national HCV treatment programme are sofosbuvir + daclatasvir, sofosbuvir/velpatasvir, sofosbuvir/ledipasvir and dasabuvir + ombitasvir/paritaprevir/ritonavir. HCV testing in the public sector is currently limited. Although the national guidelines recommend treatment for all patients with HCV regardless of disease stage, patients with advanced liver disease and extrahepatic manifestations of HCV are given priority due to the lack of capacity to treat them all. Generic medicines at lower costs are available in Ukraine since 2017. A pangenotypic regimen of sofosbuvir + daclatasvir from Mylan is procured using international procurement mechanisms at around US$ 90 per treatment course. Generic sofosbuvir/ledipasvir is also available at the same price. Sofosbuvir/velpatasvir, howewer, is three times more expensive. About 9300 patients were receiving treatment in Ukraine within the framework of the national treatment programme at the end of 2018, and procurement of around 15 000 HCV treatment courses was scheduled at the end of 2019. More than 5000 patients, representatives of the most vulnerable populations such as PWID, people with comorbidities and people in prisons also received treatment within the framework of the APH treatment programme aimed at integrating HCV testing and treatment for key populations in harm reduction programmes run by the organization in all Ukrainian regions. Some of the challenges identified include budget constraints for the national programme, weak surveillance systems, high prices and limited access to diagnostics, reluctance from some medical practitioners to prescribe generic products and financial barriers to accessing services.

Successful approaches share common enablers

These country experiences represent a diverse range of contexts in relation to national plans and strategic approaches to allocate resources, obtain lower prices, address patent and regulatory barriers, and engage with civil society organizations. Taken together, these experiences draw attention to some common public health building blocks that are essential for achieving universal access to HCV diagnostics and treatment.

i. Adopting a public health approach focused on universal health coverage

Countries such as Egypt have demonstrated that, to scale up the public health response to viral hepatitis, as part of broader universal health coverage, strong government leadership can accelerate massive, rapid testing, treatment and change. Egypt's countrywide effort to screen the population for hepatitis infection, and provide treatment for all was coordinated with broader efforts to screen for noncommunicable diseases such as hypertension and diabetes within a universal health coverage approach. Similarly, countries such as Ukraine are leveraging existing HIV investments to expand harm reduction and HCV services to key populations. China has integrated some DAAs into the national health insurance scheme. High-level government commitment has also played a key role in Mongolia, where a nationwide screening and treatment programme was implemented as part of universal health coverage.

ii. Simplifying hepatitis C testing and delivery

The successful example from Egypt also highlights the importance of scaling up access to simplified and affordable screening and diagnostics for hepatitis C, in order identify people with hepatitis C infection and link them to care. Mongolia and Pakistan are similarly undertaking large-scale public health screening efforts. Rwanda is leveraging its decentralized health-care delivery network to provide universal hepatitis C screening for the adult population using RDTs at the primary care level.

iii. Accelerating quality assurance and product registration/approval

More countries have access to treatment options, including generic products, that meet international quality, safety and efficacy standards. Countries such as Egypt and Morocco are prioritizing product registration of DAAs, following the updating of their treatment guidelines, in order to facilitate immediate access to these products and make it possible to scale up coverage rapidly. Other countries such as India and Ukraine have registered multiple suppliers and products to help ensure competition, drive down prices and minimize service disruptions. However, product registration remains slow in many other countries due to a number of factors, including requirements for generic manufacturers to provide locally obtained clinical trial data (even for WHO-prequalified products), low demand and uptake, and lack of information on opportunities to procure quality generic products. In 2019, there were 62 low- and middle-income countries that had registered at least one version of sofosbuvir + daclatasvir, sofosbuvir/ledipasvir

or sofosbuvir/velpatasvir from originator or generic manufacturers; as compared to 32 in 2017. If pangenotypic regimens alone are considered, only 46 countries that had registered at least one product from originator or generic companies with their national regulatory authorities.

iv. Obtaining continued price reductions and addressing patent-related barriers

Countries are adopting different strategies to continue to drive down prices, including by expanding generic competition, and issuing public health-oriented licensing. In Malaysia, the government issued a compulsory license to enable local companies to manufacture sofosbuvir or import it into the country under certain conditions. Subsequently, Gilead included Malaysia in their voluntary licensing territory. Overall, access to generic DAAs under import through the compulsory license resulted in a substantial decrease in prices. In Egypt and India, local production of generic medicines has made these treatments available at very low cost. Further efforts will be needed to ensure that all those in need, particularly the most vulnerable, can benefit from these prices.

v. Engaging with civil society and leaving no one behind

Civil society organizations in many countries are playing a key role, both in terms of advocacy and in direct service delivery to key populations. For example, patent oppositions to sofosbuvir filed by civil society organizations in Brazil, China, Egypt and Ukraine helped to facilitate the availability of generic products in these markets. Organizations such as Coalition PLUS in Morocco and Médecins Sans Frontières (MSF) in India and Pakistan are supporting the delivery of HCV and harm reduction services for key populations, in particular, PWID. Georgia's national programme is rolling out decentralized service delivery for patients with chronic HCV at both primary health-care services and harm reduction centres. It is important to strengthen data and targets for these populations.

vi. Leveraging financing and procurement options

Domestic financing for the HCV response in low- and middle-income countries remains limited overall, and there are few international financing sources. Many countries have committed resources to providing HCV diagnosis and treatment free of charge in the public sector as part of dedicated hepatitis programme budgets and/or inclusion in national health insurance schemes. For example, in Morocco, the government has allocated resources to purchase diagnostics and treatment in order to begin rolling out a public sector programme in the main national hospitals. Some international financing sources, such as Unitaid, are also supporting countries to fast-track their programmes. International procurement mechanisms and pooled procurement strategies are equally critical to obtain efficient delivery.

The following chapters describe these key enablers in further detail and highlight the main achievements and barriers in the different areas.

© WHO / Blink Media – Juliana Tan

IV Key enablers for accelerating universal access to hepatitis C diagnostics and treatment

This section documents the progress and challenges in relation to the key enablers of scaling up access to hepatitis C diagnostics and treatment in different settings – the availability of simplified norms and standards and quality-assured product options; their affordability in different country contexts; equity in access for all populations in need; and efficiency in delivery.

IV.1 Availability: simplified norms and standards, more and improved product options

The past 6 years have witnessed major evolutions in the field of HCV therapeutics. Until 2013, the standard of care to treat HCV infection involved a 24–48-week long interferon-based regimen administered by injection. The regimen was toxic, costly, challenging to deliver at scale, and had cure rates of less than 50% *(10)*. The introduction in 2014 of DAAs – a new class of medicines with an oral treatment course of 8–12 weeks, high cure rates and few side-effects – revolutionized the treatment of HCV infection and brought wide scale up of treatment access within reach. WHO released the first-ever guidelines on HCV screening, care and treatment for low- and middle-income countries in 2014, and added the first DAAs to the WHO Essential Medicines List in 2015.

In 2017, WHO published the first guidelines on testing for hepatitis B and C infection *(11)*. These guidelines reviewed the most accurate testing strategies for countries to follow, recommending one serological assay to screen for HCV infection, followed by detection of HCV RNA or HCV core antigen to diagnose chronic HCV infection, and assessment of liver disease using non-invasive tests. HCV NAT is the preferred option for assessment of cure. Another important advance is the finding that POC viral load testing can detect active infection from a fingerstick sample, which represents an improvement over antibody-based tests that only indicate past or previous exposure *(38)*. The use of fingerstick sampling also improves service quality for key populations, as compared to venepuncture.

The 2018 update to the WHO guidelines introduced further simplifications in the delivery of diagnosis and treatment services *(12)*. The new guidelines adopt a "treat all" approach that recommends that all persons living with chronic HCV infection (with the exception of pregnant women and children under 12 years) should start treatment with DAAs immediately, irrespective of disease stage. The guidelines also recommend the use of pangenotypic regimens, which are effective against all six major subtypes of HCV with a success rate of over 90%. Wider access to pangenotypic DAAs can greatly facilitate the scale up of treatment in low-income settings by simplifying treatment initiation and delivery for patients, as well as procurement and distribution processes for national programmes. The DAAs, including pangenotypic options, which are included in the WHO Essential Medicines List, are noted in Table 4 *(39)*. The list is updated every two years.

The new 2018 guidelines also enabled major simplifications in the screening and diagnostic tests required for treating hepatitis C. The recommendation to "treat all" with DAAs removes the need for staging of liver disease, and the recommendation to use pangenotypic regimens removes the need for genotype testing prior to initiating treatment. Both of these are complex procedures that require specialized laboratory services that have been scarcely available in low-income settings. The screening and diagnosis of HCV now involves a two-step algorithm, comprising an antibody test followed by a viral load test for confirmation. RDTs are becoming more widely available and can enable simplified delivery of diagnostic services at decentralized levels.

Table 4: Direct-acting antivirals that are on the twenty-first edition of the WHO Model List of Essential Medicines, 2019 *(39)*

WHO guidelines recommend the use of pangenotypic DAA regimens for the treatment of persons aged 18 years and above with chronic HCV infection.

For adolescents with chronic HCV infection aged 12–17 years or weighing at least 35 kg, WHO-recommended treatment regimens are genotype-specific.

Pangenotypic DAA-based regimens should be considered as therapeutically equivalent to each other for the purposes of selection and procurement at the national level.

Direct-acting antiviral regimen	Dose form and strength
Pangenotypic direct-acting antiviral combinations	
Daclatasvir*	Tablet 30 mg; 60 mg (as hydrochloride) *pangenotypic when used in combination with sofosbuvir
Glecaprevir + pibrentasvir	Tablet: 100 mg + 40 mg
Sofosbuvir*	Tablet 400 mg *pangenotypic when used in combination with daclatasvir
Sofosbuvir + velpatasvir	Tablet 400 mg + 100 mg
Non-pangenotypic direct-acting antiviral combinations	
Dasabuvir	Tablet: 250 mg
Ledipasvir + sofosbuvir	Tablet: 90 mg + 400 mg
Ombitasvir + paritaprevir + ritonavir	Tablet: 12.5 mg + 75 mg + 50 mg

Data source: Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection. Geneva: WHO; 2018

IV.2 Quality: Meeting quality assurance and product regulation standards

Large-scale roll-out of HCV diagnostics and treatment in low- and middle-income countries must be accompanied by efforts to ensure compliance with international quality assurance standards and national regulatory procedures. The availability of quality-assured diagnostics and generic products is steadily increasing, offering a tremendous opportunity to scale up access to diagnosis and treatments that are reliable and safe. On the other hand, a large number of unregulated HCV RDTs are also available for purchase through popular e-commerce websites at low prices. Product registration and quality assurance are thus critical to ensure service quality.

More products and suppliers are meeting international quality assurance standards

By seeking WHO prequalification of their diagnostic and treatment products, manufacturers can ensure that countries have access to a wide range of commodities that meet unified standards of acceptable quality, safety and efficacy (Box 5).

Box 5
WHO-supported processes for international quality assurance and product regulation

WHO supports a number of international processes to facilitate access to high-quality products.

The WHO **Prequalification programme** is a service provided since 2001 by WHO to facilitate access to medicines and diagnostics that meet unified standards of quality, safety and efficacy/performance. It was initially established in response to the HIV epidemic to support international organizations to identify quality-assured antiretroviral medicines for low-income countries. It now covers the assessment of a wide range of finished pharmaceutical products and active pharmaceutical ingredients in several therapeutic areas, quality control of laboratories, as well as a growing number of in vitro diagnostics (IVDs). It works in cooperation with national regulatory agencies and partner organizations to conduct assessment and inspection activities (as well as a performance evaluation for diagnostics), build national capacity for manufacture, regulation and monitoring of medicines, and register those medicines quickly.

The WHO **Collaborative Procedure for Accelerated Registration** supports national drug regulatory authorities to facilitate timely in-country assessment and registration of finished pharmaceutical products that have been prequalified by WHO or approved by another internationally recognized stringent regulatory authority (such as the US Food and Drug Administration [US FDA] or the European Medicines Agency [EMA]), thereby ensuring that medicines can reach patients more quickly. It also minimizes the costs and time taken to register medicines in-country by taking advantage of assessments and inspections that have already been conducted as part of international processes, in particular, in low-income countries where regulatory resources may be scarce. For diagnostics, the process was piloted in 2019 and will be implemented in interested jurisdictions.

The **Expert Review Panel** (ERP) is an independent advisory body of technical experts hosted by WHO. The Panel provides a service to international procurement or funding organizations, such as the Global Fund and Unitaid. It assesses the potential risks and benefits associated with the use of pharmaceutical or diagnostic products that do not meet all stringent quality requirements and provides advice to support procurement decisions on a time-limited basis, during which time the products are expected to progress in a stringent regulatory pipeline such as WHO prequalification.

WHO also supports manufacturers to conduct post-market surveillance of IVDs that have been found to meet quality, safety and performance requirements by the WHO Prequalification programme. Users in public and private sector testing programmes are encouraged to report any feedback to the manufacturer and national regulatory authorities in a timely manner. Users may also provide feedback to WHO. WHO oversees the manufacturer's investigation, and any correction and/or corrective action that has been taken by the manufacturer.

In recent years, the availability of treatment options that meet international quality standards is increasing overall. As of 2017, five single-component DAAs and six fixed-dose combinations had received regulatory approval from at least one stringent authority. No new molecules have been launched or received approval since then.

The total number of generic sources from which quality-assured DAAs are available is also steadily increasing. In 2016, no generic DAAs were WHO-prequalified or approved by a stringent regulatory authority. By early 2018, WHO had prequalified three sofosbuvir tablets from generic manufacturers (Cipla, Hetero and Mylan). As of early 2020, two additional generic manufacturers (Strides and European Egyptian Pharmaceutical Ind. Co.) supplied WHO-prequalified sofosbuvir. Similarly, in 2018, WHO-prequalified daclatasvir tablets were available only from the originator manufacturer (BMS) and no generic manufacturer. By early 2020, WHO-prequalified daclatasvir was also available from generic manufacturers.

As of end-2020, WHO-prequalified fixed-dose combinations of sofosbuvir/daclatasvir, sofosbuvir/ledipasvir and sofosbuvir/velpatasvir were also available from one generic manufacturer. It is important to note that no fixed-dose combination of glecaprevir/pibrentasvir is WHO prequalified, either by the innovator or by any generic producer.

The generic DAAs that are prequalified by WHO or reviewed by the ERP as of 2020 are summarized in Table 5 *(40,41):*

Table 5: Status of generic direct-acting antivirals that are prequalified by WHO or reviewed by the Expert Review Panel (ERP), December 2020

Direct-acting antiviral regimen	Dose form and strength	
Sofosbuvir	WHO-prequalified	Cipla Hetero Mylan Strides Pharco/European Egyptian Pharmaceutical Ind. Co. (EEPI)
	ERP-reviewed	Cipla Hetero Mylan Strides
Daclatasvir	WHO-prequalified	Cipla Hetero Mylan Laurus
	ERP-reviewed	Cipla Hetero Mylan
Sofosbuvir + daclatasvir (co-blistered)	WHO-prequalified	Cipla
	ERP-reviewed	Cipla
Sofosbuvir/daclatasvir	WHO-prequalified	Mylan
	ERP-reviewed	Mylan
Sofosbuvir/ledipasvir	WHO-prequalified	Mylan
	ERP-reviewed	Mylan
Sofosbuvir/velpatasvir	WHO-prequalified	Mylan
	ERP-reviewed	Mylan
Glecaprevir/pibrentasvir	WHO-prequalified	None
	ERP-reviewed	None

Source: WHO prequalification of medicines/finished pharmaceutical products [database] (https://extranet.who.int/prequal/content/prequalified-lists/medicines, accessed 16 January 2021).

Information reported by manufacturers suggests that their market outreach is also increasing. For example, Mylan and Hetero are both present in the international market for several DAA fixed-dose combinations. Pharco, which was initially selling its products almost exclusively in Egypt, obtained WHO prequalification for sofosbuvir in December 2018 and reports exporting to other countries, including Malaysia and Nigeria. A new initiative was launched by Egypt in 2019 to support hepatitis C testing and treatment for 1 million people in 14 African countries that have a significant hepatitis burden with the involvement of an Egyptian generic manufacturer.

In terms of diagnostic tests (Tables 6 and 7), as of mid-2020, WHO had prequalified eight antibody detection HCV assays (four RDTs, three enzyme immunoassays and one line immunoassay), four HCV NATs that allow for confirmation of chronic HCV infection, and one HCV antigen assay for detection of HCV core antigen. Two of the NATs can also be used at POC. The HCV core antigen assay is recommended by WHO as an alternative to HCV RNA NAT for confirmation of viraemic infection, but not as a test of cure. Of the HCV antibody RDTs reviewed by the ERP for diagnostics, one test has been classified as being eligible for limited procurement.

Table 6: Status of in vitro diagnostics (IVDs) for HCV that are prequalified by WHO, 2020

Product name	Manufacturer	Date product prequalified
Murex anti-HCV (version 4.0)	DiaSorin South Africa (Pty) Ltd.	2015
INNO-Lia HCV Score	Fujirebio Europe NV	2015
Bioline HCV (formerly SD BIOLINE HCV)	Abbott Diagnostics Korea Inc. (formerly Standard Diagnostics, Inc.)	2016
OraQuick HCV rapid antibody test kit	OraSure Technologies, Inc.	2017
Xpert HCV Viral Load with GeneXpert Dx, GeneXpert Infinity-48s, and GeneXpert Infinity-80	Cepheid AB	2017
INNOTEST HCV Ab IV	Fujirebio Europe NV	2018
Rapid anti-HCV test	InTec Products, Inc.	2019
ARCHITECT HCV Ag assay	Denka Seiken Co., Ltd, Kagamida Factory	2019
Abbott RealTime HCV	Abbott Molecular Inc.	2019
Monolisa HCV Ag-Ab ULTRA V2	Bio-Rad	2020
STANDARD Q HCV Ab test	SD Biosensor, Inc.	2020
Alinity m HCV	Abbott Molecular Inc.	2020
Genedrive HCV ID Kit	Genedrive Diagnostics Ltd	2020

Table 7: Status of in vitro diagnostics (IVDs) for HCV that are reviewed by the Expert Review Panel for Diagnostics, 2020

IVD name	Manufacturer	Risk category	Year of review
On Site HCV Ab Combo Rapid Test, CS	LAB-Stix Diagnostics	4	2015
On Site HCV Ab rapid test, DS	LAB-Stix Diagnostics	4	2015
On Site HCV Ab rapid test, CS	LAB-Stix Diagnostics	4	2015
Rapid Anti HCV test	Intec	4	2015
BioTracer HCV Rapid Card	Bio Focus Co. Ltd	4	2015
SD Bioline HCV test	Standard Diagnostics	3	2015
Generic HBV charge viral/GHBV-CV	Biocentric	3	2018
HCV/HBsAg/HIV combo rapid test cassette	Hangzhou Biotest	4	2018

Product registration with national regulatory authorities is increasing

DAAs need to be registered with the national regulatory authority by the manufacturer in order to be sold in a country. If access to generic medicines is possible, registration of products from as many manufacturers as possible will increase competition and lower prices. Registration reports from companies show some increase of country registration in low-income, lower-middle-income and upper-middle-income countries, from both originator and generic manufacturers.

The overall number of countries with at least one registered DAA is increasing steadily, yet overall progress remains slow and the potential of the generic market has not yet been fully exploited. Some of the challenges include requirements for generic manufacturers to provide locally obtained clinical trials data (even for WHO-prequalified products), low demand and uptake, and lack of information on opportunities to procure quality generic products. Based on information collected from companies in 2019 (Table 8), a total of 62 countries (low-income, lower-middle-income and upper-middle-income) had registered at least one version of sofosbuvir + daclatasvir, sofosbuvir/ledipasvir or sofosbuvir/velpatasvir from originator or generic manufacturers as compared to 32 in 2017. Further, updated information available from the MPP indicates that for daclatasvir, an additional 16 countries had also registered generic sources of daclatasvir as of March 2020, bringing the total to 32, and companies had filed for the same in another 22 countries *(42)*.

If sofosbuvir/ledipasvir is excluded and only pangenotypic regimens considered, the total number of countries where at least one DAA was registered in 2019 was 46, as compared to only 16 countries in 2017. Generic sofosbuvir + daclatasvir was registered in 10 countries by 2019, generic sofosbuvir/ledipasvir in 15 countries and generic sofosbuvir/velpatasvir in six countries. In 2017, these were registered in five or fewer countries.

Countries are using various approaches to ensure timely registration of drugs and diagnostics to support programme scale up. For example, Botswana and Zambia have used the WHO Collaborative Procedure for Accelerated Registration for registration of sofosbuvir. Other countries such as Cambodia, Myanmar, Nigeria and Viet Nam are using drug waivers to expedite access to DAA regimens while in the process of obtaining full registration, supported by documentation that indicated the approval of originator and generic DAAs by the WHO-prequalification department. Registering multiple suppliers for each product can also help to ensure competition and low prices, and minimize supply disruptions. Some of the largest price decreases have been seen in countries such as India where multiple suppliers and products are registered *(43)*.

In the area of IVDs, several jurisdictions that are members of the International Medical Device Regulatory Forum possess adequate capacity for regulation of medical devices, including IVDs. Whereas other jurisdictions are still setting up or implementing regulatory frameworks, most countries lack the capacity to efficiently regulate their market. This often results in a lack of transparency and complex pseudo-regulatory pathways, creating barriers to effectively leverage existing evidence for quality-assured products. WHO will be working with Member States to facilitate in-country registration of prequalified diagnostics through the Collaborative Registration Procedure to support efforts at increasing access to quality-assured diagnostics, including those for hepatitis C.

Table 8: Total number of low-income, lower-middle-income and upper-middle-income countries with registered DAAs, 2017 and 2019

DAAs	2017			2019		
	Countries with generic sources registered	Countries with originator sources registered	Total number of countries with registered sources	Countries with generic sources registered	Countries with originator sources registered	Total number of countries with registered sources
Daclatasvir	2	10	12	16 (+ additional 16 as of March 2020)	14	30
Sofosbuvir	23	31	54	29	32	61
Sofosbuvir + daclatasvir	1	14	15	10	17	27
Sofosbuvir/ledipasvir	5	24	29	15	36	51
Sofosbuvir/ velpatasvir	1	2	3	6	28	34

Data source: Report of the WHO survey on access to DAAs, 2019 and Medicines Patent Pool, 2020[42]

IV.3 Affordability: Lowering prices and patent-related barriers

The price of products is influenced by a range of factors, including the country's market size, in-country patent situation of the different medicines, availability of quality-assured generic products, local production capacity, and the country's pricing policies. While the overall prices of HCV diagnostics and treatment continue to fall, wide differences persist across regions and countries. Patent-related barriers are one of the major factors causing such price variability, as well as supporting a shift to a higher-volume, lower-price and high-value market.

The various dimensions of product pricing and the lack of homogeneity in price reporting (different International Reporting Terms [incoterms]) make it challenging to systematically analyse prices across countries and settings. Where available, prices are reported per 28-day supply (bottle) or as the total costs per treatment course (12–14 weeks' supply). Information related to product source (originator or generic), quality assurance (WHO-prequalified or approval by at least one stringent regulatory authority), and sector (public or private, import or export) is indicated where relevant. Further details can be found in Annex 1 (Drug profiles).

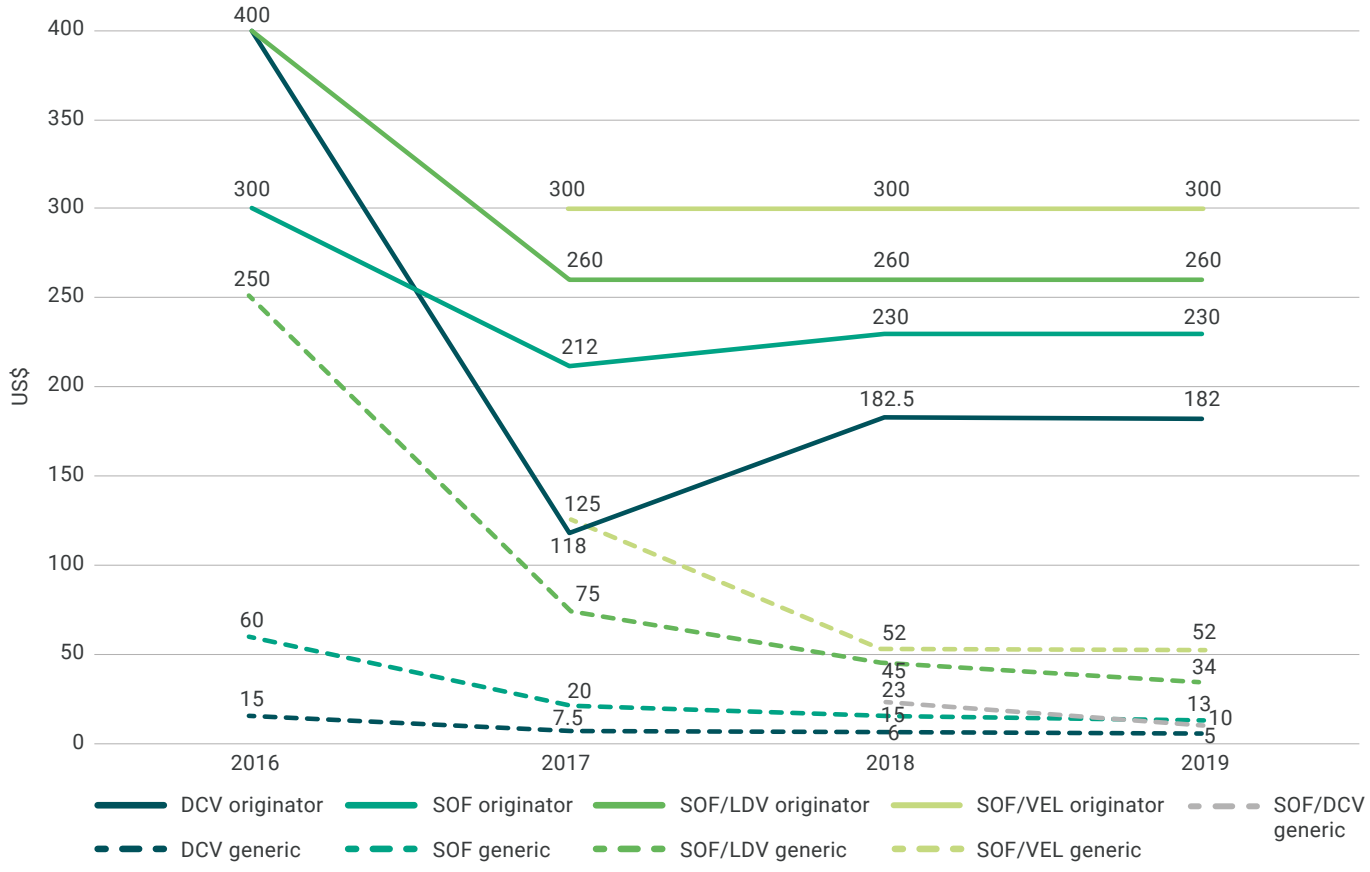
IV.3.1 Prices of hepatitis C treatment

Treatment prices continue to fall overall, but wide disparities persist among countries

Since 2015, increased competition from generic products has continued to drive down the prices of DAAs, especially in low- and middle-income countries where generic products are available. Since 2018, the prices of generic products have continued to decline sharply, while the prices of originator products have largely remained the same or seen smaller declines. A 2020 market report on hepatitis C commodity pricing from CHAI reports that low- and middle-income countries can now aim to achieve prices less than US$ 100 per patient course for 12 weeks of treatment with WHO-prequalified generic sofosbuvir and daclatasvir, including a price as low as US$ 60 per patient course – among the lowest recorded prices for hepatitis C treatment that meets international quality assurance standards *(31)*.

Countries such as India, Egypt and Pakistan are paying even lower prices for some locally manufactured and locally approved products. However, the range of prices paid by countries remains wide, and upper-middle-income countries have been unable to benefit from price reductions, as shown in Fig. 3 and 4 and further described in the section below.

Fig. 3: Trends of the lowest prices of direct-acting antivirals per 28-day supply, 2016–2018



Source: Report of the WHO survey on access to DAAs, 2019

The price of DAAs varies greatly between originator and generic products, and across country income levels, as a result of differences in individual country contexts. In countries that have been able to benefit from voluntary licensing agreements or other price reduction strategies such as negotiation of lump sum agreements, local production and increased competition has continued to drive down prices (although not all locally manufactured products may be WHO prequalified or approved by other stringent regulatory authorities). Countries where patents prevent market entry of generic products continue to pay prices that prohibit population-wide access to hepatitis C treatment.

The price trends and variations are presented by DAA below.

Sofosbuvir. The overall price of sofosbuvir, the mainstay of current HCV regimens, has continued to fall steeply. Between 2016 and 2018, the lowest reported price of originator sofosbuvir from Gilead dropped from US$ 300 to US$ 230 per 28-day supply. Lower prices at US$ 212 were also reported in 2017 from some countries. The lowest reported price of generic sofosbuvir dropped by 75% from US$ 60 to US$ 15 per 28-day supply over the same time period. The lowest generic price of US$ 15 per 28-day supply was reported in the public sector in India, from Mylan, for a WHO-prequalified product.

Upper-middle-income countries continue to pay substantially higher prices. In the Russian Federation, which is not included in the voluntary licensing agreement with Gilead, the price of sofosbuvir decreased from US$ 3338 in 2018 to US$ 1099 per 28-day supply in 2020 *(37)*. The availability of generic DAAs is limited in the Russian Federation (daclatasvir is manufactured by a local generic manufacturer under an exclusive license from the originator company BMS) *(35)*. Funding for hepatitis C treatment programmes is limited, decentralized and decreasing. Access to DAAs in the public health-care system has been rationed (rationing criteria depend on the region). The FAS proposed draft compulsory licensing legislation, but this was not supported by the Parliament *(36)*. Civil society has also called for compulsory licenses, but none have been issued to date. Patent oppositions to sofosbuvir patents have been filed both by civil society and by a domestic generic company, and the national patent office has required patent claims to be narrowed *(44)*. The patent on sofosbuvir has recently been extended by 3 years in a patent term extension *(45)*.

In China, following a civil society patent opposition, the originator withdrew the majority of claims from the main compound patent on sofosbuvir in 2018. The remaining claims covering metabolites were not expected to block generic entry as Chinese national patent law does not recognize metabolites as a basis for infringement suits *(46)*. However, other patents covering sofosbuvir, such as prodrug, crystalline form and manufacturing process patents are in force *(47)*. The first generic sofosbuvir product was approved in March 2020; however, the patent opposition remains contested and the product is not yet available on the market as of mid-2020. Originator sofosbuvir is available for US$ 2747 per 28-day supply.

In Brazil, the patent status of sofosbuvir has been unclear ever since the medicine first entered the market. A pharmaceutical patent can be granted in Brazil only if approved by both the national patent office (*Instituto Nacional de Propiedade Industrial;* INPI) and the national health regulatory agency (*Agência Nacional de Vigilância Sanitária;* ANVISA). Following patent oppositions by civil society, ANVISA refused to approve a key sofosbuvir patent, on the basis that the product lacked novelty and inventiveness. The refusal to grant the patent was overturned in court. After this, the patent approval decision was in turn suspended by another court. Meanwhile, a generic version had been developed by a domestic public–private consortium comprising local private pharmaceutical companies and the government laboratory Farmaguinhos. This consortium offered a price one quarter of that offered by Gilead and, in late 2018, the MoH began purchasing the consortium's product. Gilead has subsequently competed for MoH purchases with lower prices *(25)*. By 2018, generic sofosbuvir was available in Brazil at US$ 235 per 28-day supply.

In Malaysia, which took a different approach in 2017 through compulsory licensing, generic sofosbuvir is imported for US$ 34 per 28-day supply, as compared to US$ 11 200 reported prior to 2017 for the originator version.

Daclatasvir. The overall price of daclatasvir has also continued to fall. Between 2016 and 2018, the lowest reported price of originator daclatasvir from BMS dropped from US$ 400 to US$ 182 per 28-day supply. Lower prices at US$ 118 were also reported in 2017 in some countries. The lowest reported price of generic daclatasvir dropped by 60% from US$ 15 to US$ 6 per 28-day supply over the same time period. The lowest generic price was found in the public sector in India, from Mylan, for a WHO-prequalified product. In China, originator daclatasvir is available for US$ 182 per 28-day supply. In contrast, in the Russian Federation, the price of originator daclatasvir was US$ 1188 in 2018 and US$ 587 in 2020 per 28-day supply from BMS *(37)*.

Sofosbuvir/daclatasvir fixed-dose combination. In 2018, a generic fixed-dose combination of sofosbuvir/daclatasvir became available from several generic companies in Egypt, India, Morocco and Pakistan. The lowest price for an ERP-reviewed product was available in the public sector in India at US$ 20–25 per 28-day supply. In Egypt and Pakistan, locally manufactured sofosbuvir/daclatasvir are available at US$ 16 and US$ 7–10 per 28-day supply, respectively, or a treatment course of less than US$ 50. In contrast, the product in Morocco was available at US$ 330 per 28-day supply. As of end 2020, a WHO-prequalified generic fixed-dose combination was available from Mylan at US$45 per 28 day supply.

Sofosbuvir + daclatasvir. India has the lowest reported prices for the generic non-fixed-dose combination of sofosbuvir and daclatasvir at US$ 15 and US$ 6 per 28-day supply for a locally manufactured product, or US$ 61 per treatment for WHO-prequalified products. A WHO-prequalified generic product (co-pack) is available from Cipla at a reported price of US$ 45–50 per 28-day supply. In Ukraine, where generic medicines are available since 2017, the sofosbuvir + daclatasvir combination can be purchased at around US$ 100 per treatment course. In the Russian Federation, where only innovator products are available, the reported price for sofosbuvir from Gilead and daclatasvir from BMS is around US$ 5058 per 3-month treatment course in 2020 *(see Fig. 4.1)*. In China, the reported price for sofosbuvir from Gilead and daclatasvir from BMS is around US$ 8787 per 3-month treatment course in 2020.

Sofosbuvir/ledipasvir. The lowest reported price of originator sofosbuvir/ledipasvir from Gilead dropped from around US$ 400 to US$ 300 per 28-day supply in low-income countries between 2016 and 2017, and has remained unchanged since. The lowest reported price of the generic version of an ERP-reviewed product dropped by 82%, from US$ 250 to US$ 45 per 28-day supply over the same time period, also from Mylan in India. In Ukraine, generic sofosbuvir/ledipasvir is available at US$ 34 per 28-day supply.

Prices are higher in many other countries. In Mongolia, for example, generic sofosbuvir/ledipasvir is available at US$ 80 per 28-day supply, equivalent to US$ 240 for a 3-month course. It should be noted that sofosbuvir/ledipasvir is not pangenotypic and its effect is suboptimal in cases of infection with genotype 3, particularly in patients with cirrhosis. As of end 2020, a WHO-prequalified generic fixed-dose combination of sofosbuvir/ledipasvir was available from Mylan at US$40-50 per 28 day supply in the public sector.

Sofosbuvir/velpatasvir. Between 2017 and 2018, the lowest reported price of originator sofosbuvir/velpatasvir from Gilead remained unchanged at US$ 300 per 28-day supply available in low-income countries. The lowest prices reported by a country were from India at US$ 55 per 28-day supply from Mylan, which has filed for WHO prequalification, and from Pakistan at US$ 52 per 28-day supply. In Ukraine, generic sofosbuvir/velpatasvir is available at US$ 100 per 28-day supply. In Brazil, the MoH negotiated a price of US$ 1470 per treatment course with the originator company, or US$ 490 per 28-day supply *(see Fig. 4.2)*. As of end 2020, a WHO-prequalified generic fixed-dose combination of sofosbuvir/velpatasvir was available from Mylan at US$50-80 per 28 day supply in the public sector.

Glecaprevir/pibrentasvir. There are no WHO-prequalified or ERP-reviewed generic versions of glecaprevir/pibrentasvir. The price for glecaprevir/pibrentasvir from the originator AbbVie was US$ 5071 per 28-day supply or US$ 10 142 per 8-week course of treatment in the Russian Federation in 2018. In 2020, the price reported in the Russian Federation is US$ 2668 per 28-day supply.

Box 6
Support for market shaping from the Clinton Health Access Initiative

Since 2015, CHAI has been supporting low- and middle-income countries to scale up access to hepatitis C treatment through market shaping and price negotiations, and advocating for domestic and international financing efforts. CHAI has also provided technical support to ministries of health to develop and cost national hepatitis plans.

In 2020, CHAI released a first edition of a market report on HCV diagnostics and treatment. The report provides a detailed overview of the supplier landscape for WHO-recommended HCV diagnostics and medicines, highlights global benchmark prices for different products, describes price and volume trends, and provides information on supplier-specific pricing structures *(31)*. The CHAI report complements this WHO global progress report by providing comprehensive supplier-side information and market intelligence, and relevant data from the CHAI report are cited here where applicable.

Figure 4.1: Variations in reported price in the WHO survey among 12 countries for a 3-month course of sofosbuvir and daclatasvir (in US$)

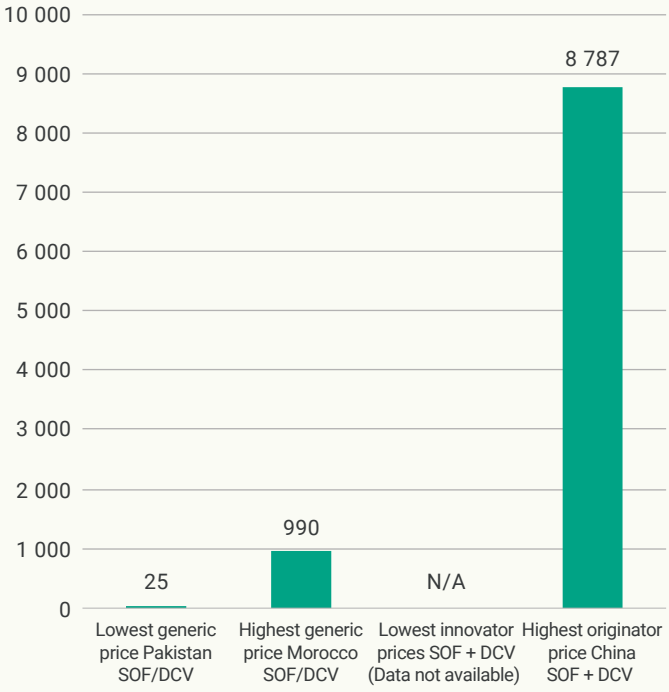
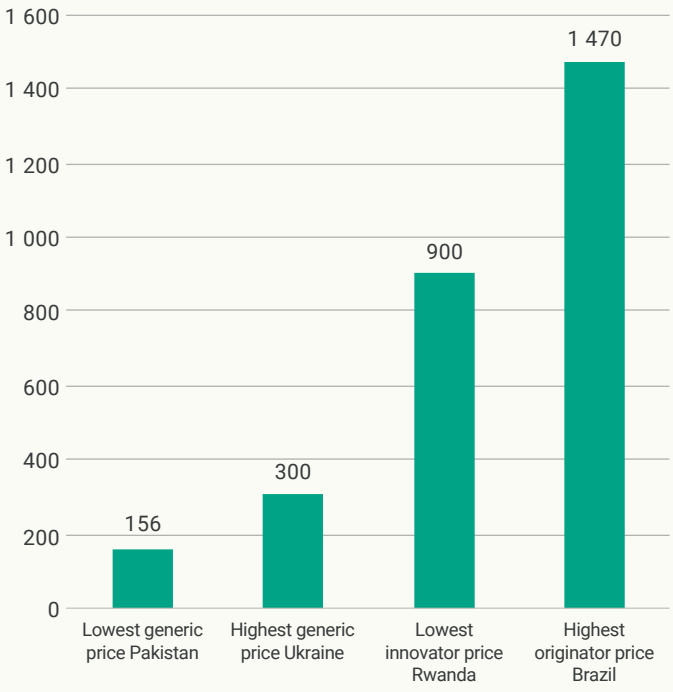


Figure 4.2: Variations in reported price in the WHO survey among 12 countries for a 3-month course of sofosbuvir/velpatasvir (in US$)



Data source: Report of the WHO survey on access to DAAs, 2019

Box 7
Medicines Patent Pool facilitates access to hepatitis C medicines in low- and middle-income countries

The MPP is a non-profit organization backed by the United Nations (UN). It facilitates access to medicines for treating major diseases such as HIV, TB and hepatitis C in low- and middle-income countries. It has recently expanded the mandate to other disease areas as well, to improve access to other essential medicines, such as those that are on the WHO Essential Medicines List. The MPP accelerates and expands access to essential medicines through public health-oriented licensing and patent pooling. It works with a wide range of partners, including governments, UN organizations, civil society and patient groups, originator and generic manufacturers, and procurement agencies to ensure that people in need of treatment get timely access to more affordable WHO-prequalified products.

As of June 2020, the MPP has eight sub-licensees and holds three license agreements for DAAs: for daclatasvir with BMS; for glecaprevir/pibrentasvir with AbbVie; and for ravidasvir, an investigational pangenotypic DAA, with Pharco Pharmaceuticals *(48)*. By March 2020, more than 950 000 courses of treatment of generic daclatasvir had been distributed through MPP licensees across 28 countries *(42)*. The majority of these sales were in India and Pakistan. In addition, fixed-dose formulations of sofosbuvir/daclatasvir have been developed by three MPP licensees; of these, one has been prequalified by WHO, and one is pending WHO prequalification *(49)*. More than 48 000 courses of treatment of generic sofosbuvir/daclatasvir have been distributed through these licensees in Cambodia, Ethiopia, India, Lao People's Democratic Republic, Myanmar, Uganda and Viet Nam.

The MPP also supports the development of new formulations such as fixed-dose combinations or paediatric formulations.

Patent-related barriers remain a critical challenge

All new DAAs are subject to patents that can allow the patent holder to prohibit others from manufacturing, using, selling or importing the patented product, thereby influencing the product's pricing structure. As patents are territorial rights and countries use different criteria and practices for granting patents, the patent situation – and thereby the prices and affordability – for the same product can differ widely across countries.

A country's ability to access generic medicines depends on whether patents are filed and granted in the country, and – if patents are filed or granted – whether the country in question is included in the territory of the respective voluntary licensing agreements of the originator company. Under voluntary licensing agreements, either through the MPP (Box 7) or directly, a patent holder permits a generic company to manufacture and sell the patented product in a defined number of countries. Other countries not included in such voluntary licensing agreements can pursue alternative strategies to reduce prices, such as the use of flexibilities contained in the World Trade Organization Agreement on Trade-Related Intellectual Property Rights to issue a government-use or compulsory license, which enables a local company to manufacture the patented product or import it under specific conditions. Some countries also engage directly in price–volume negotiations with manufacturers.

By 2018, the originator company Gilead had signed voluntary licensing agreements with 11 generic manufacturers to produce and/or sell generic versions of sofosbuvir, ledipasvir and velpatasvir in 105 countries. The number of countries included in this agreement has remained unchanged since then, and many upper-middle-income countries such as Brazil, China, Colombia, Kazakhstan, Mexico, Russian Federation and Turkey are not included, as a result of which they are unable to import or locally produce generic versions of DAA medicines.

For glecaprevir/pibrentasvir, the originator company AbbVie signed a voluntary licensing agreement with the MPP at the end of 2018 to enable quality-assured generic manufacturers to develop and sell generic medicines containing glecaprevir/pibrentasvir in 96 low- and middle-income countries and areas. However, the countries listed above are also not included in this license agreement. Further, this licensing agreement does not include India in its licensed territory. This has discouraged many Indian generic manufacturers from producing the product, because they would not be able to register or market glecaprevir/pibrentasvir within India, which carries a large hepatitis C burden.

The originator company BMS signed a voluntary licensing agreement for daclatasvir with the MPP in 2013 that included 112 countries. In early 2020, BMS announced that the marketing authorizations for its originator product will be withdrawn or will be allowed to lapse in countries where the product is no longer routinely prescribed or where there are other therapeutic options available *(50)*. Following the withdrawal/lapse of the marketing authorization, the patents in those countries will also be allowed to lapse and will not be enforced in the interim period. This decision, which is effectively equivalent to a license expansion, has an important impact on access to daclatasvir. With this new policy, additional countries and areas, including some outside the territory licensed to the MPP, now have access to generic daclatasvir, with or without existing patents. These countries and areas include Albania, Armenia, Belarus, Bosnia and Herzegovina, Bulgaria, Chile, Colombia, Egypt, Jordan, Kazakhstan, Kosovo,[f] Kyrgyzstan, Lebanon, North Macedonia, Malaysia, Mexico, Republic of Moldova, Montenegro, Peru, Romania, Serbia, Tajikistan, Thailand, Ukraine, Uruguay and the Bolivarian Republic of Venezuela *(22)*. However, in some countries, originator registration is required for registration of the generic product, so withdrawal of the marketing authorization may hamper generic registration. After the patents lapse or are withdrawn, generics are enabled on these markets.

The patent and licensing status of hepatitis C medicines in low- and middle-income countries is summarized in Tables 9 and 10, and Fig. 5. The full list of countries and areas not included in the voluntary licensing agreements can be found in Annex 3. Additional details can be found in MedsPal, the patent database of the MPP *(51)*.

f All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

The table below summarizes the voluntary licensing agreements as of January 2020 by the originators of key HCV drugs (Gilead, BMS and AbbVie) to allow generic production for use in low- and middle-income countries *(31)*.

Where patents are not filed or granted, countries can locally produce or import generic products, making it possible to obtain HCV medicines at lower prices. For example, generic companies in Egypt, India, Morocco and Pakistan are already engaging in local production under voluntary licensing agreements. However, it should be noted that products from many local generic manufacturers have not been WHO prequalified or approved by another stringent regulatory authority to date. Price negotiations with originator companies and patent oppositions have helped to lower prices in countries such as Brazil, which are not part of voluntary licensing agreements but where oppositions filed by civil society organizations led to the rejection of some key patent applications for sofosbuvir. Upper-middle- and high-income countries are also adopting various strategies to address price-related barriers, including subscription-based models and buyers' clubs, or filing patent oppositions (Boxes 8 and 9).

Table 9: Generic licenses for key DAAs, 2020

Originator company	Direct-acting antiviral	Number of countries included in licensing/ sublicensing agreement	Number of generic sublicensee manufacturers
Gilead	Sofosbuvir Sofosbuvir/ledipasvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/ voxilaprevir	105	14
Bristol-Myers Squibb	Daclatasvir	112 + 26*	7
AbbVie	Glecaprevir/pibrentasvir	96	1

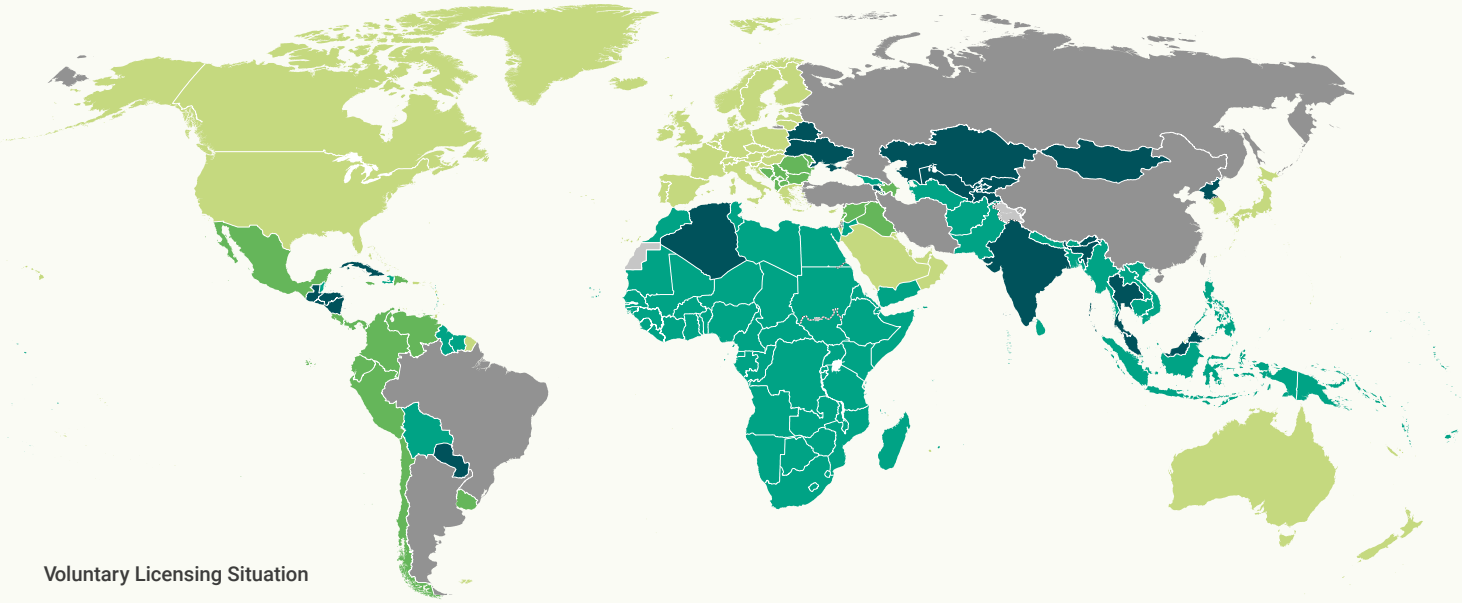
Data source: Hepatitis C Market Report. Issue 1, April 2020. Clinton Health Access Initiative, 2020 and Medicines Patent Pool (https://medicinespatentpool.org/licence-post/daclatasvir-dac/; accessed 13 July 2020)
* Refers to 26 additional countries that have access to generic daclatasvir (with or without patents) following the announcement by BMS in early 2020 that the marketing authorizations for the originator product would be withdrawn or allowed to lapse.

Table 10: Inclusion in licensing agreements of 12 selected countries, 2019

Country name	**Gilead licensing agreement** for sofosbuvir sofosbuvir/velpatasvir, sofosbuvir/ledipasvir sofosbuvir/velpatasvir/voxilaprevir	**Bristol-Myers Squibb and Medicines Patent Pool licensing agreement or patent withdrawal/lapse** for daclatasvir	**AbbVie and Medicines Patent Pool licensing agreement** for glecaprevir/pibrentasvir
Brazil	N	N	N
China	N	N	N
Egypt	Y	Y	Y
Georgia	N	Y	Y
India	Y	Y	N
Malaysia	Y	Y	N
Mongolia	Y	Y	N
Morocco	Y	Y	Y
Pakistan	Y	Y	Y
Russian Federation	N	N	N
Rwanda	Y	Y	Y
Ukraine	Y	Y	N

Data source: Report of the WHO survey on access to DAAs, 2019 and Medicines Patent Pool *(22)*.

Fig. 5: Territories licensed through Gilead, Bristol-Myers Squibb, AbbVie and Medicines Patent Pool, 2020



Data source: Medicines Patent Pool and WHO

Box 8
Upper-middle- and high-income countries are adopting various strategies to obtain price reductions

High prices continue to be a major barrier to scaling up in upper-middle-income and high-income countries. For example, in the Russian Federation, where no generic products are available as a result of high patent protection and non-inclusion of the country in voluntary licensing arrangements, the price for sofosbuvir and daclatasvir (from originator companies Gilead and BMS, respectively) is around US$ 5058 per treatment course. The price of glecaprevir/pibrentasvir from the originator company AbbVie is US$ 10 000 per treatment. In Brazil, the price for a 3-month course of treatment of sofosbuvir/velpatasvir from Gilead is US$ 1470, whereas in Lebanon the price for the same products is US$ 19 000. In many middle-income countries in Europe such as Romania, registration of generic sofosbuvir is not possible before the expiry of data exclusivity in 2022.

Some high-income countries have negotiated lump-sum agreements or subscription-based models with originator DAA manufacturers that entail paying a fixed annual amount to the originator, in exchange for a supply of as many treatment courses as are needed by the health system *(52)*. **Australia,** for example, has negotiated an agreement with Gilead wherein the government will pay approximately 1 billion Australian dollars, over 5 years, in return for an unlimited volume of DAAs. The number of treatment courses used is thus "delinked" from the overall cost, meaning that identifying and treating more HCV cases does not mean increased pharmaceutical expenditure, and that the more the number of people with HCV treated, the lower the effective cost per person. It has been estimated that this agreement equates to a per-treatment price discount of nearly 90% compared with the US list price. The agreement includes numerous originator pharmaceutical companies and a range of DAAs.

In the **United States of America,** the State of Louisiana initially considered issuing a compulsory licence on certain DAAs, but eventually negotiated a "lump-sum" agreement similar to that in Australia, with the difference that it is limited to sofosbuvir/velpatasvir *(53,54)*. The State of Washington put out a request for proposals from pharmaceutical companies that would cover both DAAs and include services such as outreach and screening *(55)*. The tender was won by AbbVie, which committed to providing medicines as well as services such as case-finding and health education, with payment taking the form of a "modified subscription model" with a cap on expenditures *(56,57)*. In part due to federal health regulations, the model is not based on a flat fee for unlimited drug volume (as in Australia). Instead, the State of Washington will pay per unit, but after a certain threshold of expenditures is crossed, the price will drop to an "extremely low" level *(58)*.

In the **United Kingdom,** an agreement was negotiated with three pharmaceutical companies, granting each a prespecified market share based on where the company was ranked in its response to a tender. The agreement includes both the provision of DAAs as well as HCV case-finding services *(59,60)*.

Other upper-middle-income and high-income countries are also using tailored approaches to obtain more affordable prices for hepatitis C medicines. In **Kazakhstan,** for example, where sofosbuvir is patented, the country was able to apply a flexibility in the World Trade Organization's Agreement on Trade-Related Intellectual Property Rights to conduct successful negotiations with the originator company Gilead to import sofosbuvir through the United Nations Development Programme (UNDP) for non-commercial use. The **Netherlands** has established a commission to assess the use of compulsory licensing to obtain lower prices for hepatitis C treatment. Countries in eastern Europe and Central Asia such as **Armenia, Kyrgyzstan, the Russian Federation, Ukraine and Uzbekistan** have previously used buyers' clubs as a strategy for patient groups to obtain better prices for hepatitis C treatment through import *(61)*.

Data and market exclusivity must also be considered with regard to accessing generics. Even where relevant patents have expired or are licensed to generic manufacturers, certain "regulatory exclusivities" such as data exclusivity (a period of time during which the holder of a marketing authorization benefits from exclusive rights to the data from clinical trials) and market exclusivity (a period of time during which an applicant cannot place a generic product on the market) can prevent the national regulatory authority from approving generic versions *(62)*.

In **Ukraine,** for example, after the rejection of key patents on sofosbuvir, Gilead in 2016 challenged the registration of a generic product based on data exclusivity, resulting in the government deregistering the generic product and agreeing to procure the originator product from Gilead at a reduced price. In August 2017, Gilead extended its licensing agreements to include Ukraine, opening the market to generic imports from its Indian licensees *(63,64)*. Data exclusivity for sofosbuvir will expire in Ukraine in late 2020 and manufacturers that are not Gilead licensees would also be able to enter the market. However, for combinations of sofosbuvir with ledipasvir and velpatasvir, import will be limited to Gilead licensees for a number of years to come, as patents currently in force on ledipasvir and velpatasvir are expected to expire earliest in 2030 *(65)*.

In the **Russian Federation,** the basic patent on sofosbuvir has been partially revoked, but data exclusivity has prevented generic versions from entering the market for six years following the approval of the originator versions *(63)*.

Box 9
Patent oppositions

In some jurisdictions, patent laws allow for third parties to file patent oppositions. In these processes, the third party submits arguments to a relevant body – normally a patent office or related administrative body – regarding the validity of a patent or patent application. Depending on the jurisdiction, oppositions can be submitted while the patent office is still reviewing a patent application (pre-grant opposition), seeking to persuade the office not to grant the patent, or after the patent has been granted (post-grant opposition), seeking for the patent to be invalidated *(62)*.

Patent oppositions to hepatitis C DAAs have been filed in a number of countries (Table 11). For example, oppositions to sofosbuvir patents have been filed in Argentina, Brazil, China, the European Patent Office (EPO), India, Ukraine and the US *(66)*. Patent oppositions filed by civil society organizations have led to the rejection of some key patent applications for sofosbuvir in Brazil, China, Egypt and Ukraine, and generics have now entered the market in these countries *(25)*.

In the EPO, following opposition filings by civil society groups and other actors, the patent-holding pharmaceutical company amended the primary sofosbuvir patent with narrower claims, after which the EPO ruled that it was valid in the reduced form *(67,68)*. The EPO's decision to uphold the patent in reduced form is under appeal by some of the opposing parties, who argue that the patent should be invalidated in its entirety *(67,68)*.

Table 11: Patent oppositions ever filed as of mid-2020

DAA	Number of patent oppositions
Sofosbuvir	41
Daclatasvir	12
Velpatasvir	5
Sofosbuvir + ledipasvir	2
Sofosbuvir/velpatasvir	2
Glecaprevir	1
Ledipasvir	1
Pibrentasvir	1
Simeprevir	1

Source: MSF Access Campaign. Patent Opposition Database. Available from: https://www.patentoppositions.org/. Data cited 25 May 2020.

IV.3.2 Prices of hepatitis C diagnostics

Data on the pricing of in vitro diagnostics is limited

As hepatitis C treatment becomes more affordable and widely available, expanding access to affordable and quality-assured hepatitis C IVDs is much needed so that countries can screen large numbers of people, identify patients in need of treatment and provide appropriate care.

Data on pricing and affordability of hepatitis C IVDs is limited, reflecting a general lack of transparency in the global market *(31)*. Nevertheless, some data are available from market studies published by Unitaid, CHAI, MSF, Médecins du Monde and Treatment Action Group *(31,69–71)*. Furthermore, in 2020, prices offered by suppliers of WHO-prequalified anti-HCV RDTs ranged between US$ 1 and 8 per test. Laboratory-based immunoassays were offered at a price between US$ 1 and 2. E-commerce websites list several low-cost HCV RDTs, but these tests have not been submitted for regulatory review by any of the founding members of the Global Harmonization Task Force, thereby raising potential issues about their safety, quality and performance.

The reagent for analyser for NAT that can be used at POC to detect HCV RNA costs between US$ 14 and US$ 30 per test, plus the cost of the analyser itself, which ranges between US$ 10 000 and 25 000. In contrast, high-throughput laboratory-based analysers can cost over US$ 100 000, with reagents costing about US$ 9 to US$ 50 per test. However, overhead costs and overall staff requirements are generally higher for analysers used at POC, which have slower throughput than laboratory-based analysers. In order to contain costs while maintaining equitable access, programmes should have a combination of laboratory-based testing that can serve inpatient and other facility-based clinical care, and testing at POC, including community-based testing, for those less likely to access health facilities.

The market dynamics for hepatitis C diagnostics are dominated by a small number of companies

Diagnostic platforms may be tied to specific types of proprietary disposable components (e.g. cartridge/reagent) in the so-called "closed systems" *(31)*. Closed systems tend to allow more automated techniques performed on one instrument/analyser, for which both reagents and instruments are sourced from the same supplier. On the other hand, "open systems" are widely used in non-medical laboratories and tend to require more manual processing. Open systems allow the use of compatible reagents from alternative suppliers. The reagents for open systems may be supplied along with the test kits or may need to be sourced separately, such as primer/probe sets and extraction reagents from more than one commercial or non-commercial manufacturer. Some suppliers offer complete test kits with the necessary reagents.

Consequently, where a country acquires closed systems, these automatically put the manufacturer in a monopoly situation, as the system always has to use the reagents produced by the same manufacturer. The market for closed-system hepatitis C reagents is thus dominated by a small number of companies.

Open platforms are an opportunity for integrating routine clinical diagnosis and testing as the majority of platforms are multidisease analysers. Multidisease analysers may offer some advantages and integration allows for efficiencies and cost savings to health systems; however, in some cases, the analysers may be approved nationally for use only in one or a few of the diseases/conditions covered. Additionally, contracts with manufacturers may limit the use of multidisease analysers to one or a few diseases/conditions *(72,73)*.

Contracting models for in vitro diagnostics analysers can offer an alternative to traditional procurement contracts

Increasingly, manufacturers of analysers – such as NAT for HCV RNA – offer tiered pricing agreements to low- and middle-income countries. The most common purchasing agreements for analysers include capital (outright) purchase, leasing and reagent rental. Prices are comprehensive under reagent rental agreements, i.e. the price paid by the buyer may include, in addition to the analyser hardware, the related proprietary consumables (such as test cartridges/reagents), and services (such as installation, maintenance and training of staff). The higher cost per test result reported is offset by the incentive to keep the analyser running with no downtime. The manufacturers offer the analyser, reagents and upkeep at no upfront cost, instead charging a set price per reportable test result, and often require an advance commitment to purchase a certain minimum number of tests per year *(31,70)*.

There are strong incentives for manufacturers to offer capital (outright) purchase rather than offer reagent/rental agreements. Countries with high volumes have been able to benefit from reagent/rental and leasing agreements; however, these are not widely available to many low- and middle-income countries. Pricing schemes that require a minimum annual volume of tests may be challenging to implement for countries with nascent screening programmes and/or smaller populations. In such cases, it may be possible to pool test volumes across other disease areas that the platform covers *(31,70)*. On the other hand, minimum testing volume requirements disincentivize split tenders, and pooling of test volumes across disease areas may further increase the country's reliance on a single manufacturer. Additionally, commitment to minimum volumes requires accurate forecasting, which may also be challenging for low- and middle-income countries with nascent screening programmes.

The role of patent protection is often more complex for diagnostics

Intellectual property plays a role in access to diagnostics for hepatitis C. However, the role of patent protection is often more complex for diagnostics than it is for medicines, among other things, because many different parts of an IVD and the technique may be patented and thus the number of relevant patents can often be greater than those for a medicine.

One example is the complex landscape of patents covering polymerase chain reaction (PCR) techniques. PCR is one format/technique that forms the basis of numerous HCV NATs for diagnosis of chronic infection, especially those that allow quantitative measurement such as viral load testing. The patent landscape for IVDs containing PCR techniques is highly complex, and any new market entrant is faced with a large number of patents to navigate *(74)*. Experts argued in 2012 that the patent portfolio of the biotechnology firm Chiron "is such that literally any company that develops [...] a diagnostic test to detect and measure HCV [...] needs to license Chiron's patents" *(75)*. As of early 2020, while certain PCR-related patents have expired (such as the aforementioned patent held by Chiron on the HCV genome), others remain in force – for example, patents covering certain PCR reagents – and the global market remains an oligopoly.

In 2017, MSF conducted patent landscape analyses on PCR-based IVDs for HIV and TB, as well as a hepatitis C rapid antibody test, along with a broader literature review of patents and diagnostics *(74)*. The analysis identified 20 patents that were potentially relevant to the anti-HCV RDT (OraQuick HCV Rapid Antibody Test, sold by OraSure Technologies). It found that major diagnostics companies hold a considerable number of patents, often bundled into thickets for various instrumentation, assays, methods and software related to different aspects of the technologies, methodologies and devices *(74)*.

Another analysis by *Association de Lutte Contre le SIDA* (the Association to Fight AIDS, Morocco) examined issues relating to access and intellectual property for the FibroScan® ultrasound device and the FibroTest blood test assay (known as FibroSure in the US), both of which are used to assess the level of fibrosis (liver tissue scarring) in people living with hepatitis C as a non-invasive alternative to liver biopsy. This assessment can help guide the duration of treatment, as well as the need for additional investigations and follow up. The tests were available mainly in private laboratories unevenly distributed across the country *(76)*. Transient elastography (FibroScan®) is a specialized ultrasound machine used by trained operators in clinical settings, and is recommended by WHO as an alternative to other low-cost approaches to staging of liver disease, such as the APRI or FIB-4 score, which uses haematology and clinical chemistry assays that are routinely available in most laboratories supporting clinics at lower-level health facilities. WHO recommendations include the use of low-cost APRI score, and transient elastography where available, but has not yet reviewed the evidence for the clinical utility of FibroTest, which is recommended by professional society organizations in high-income countries.

IV.4 Equity: Addressing the needs of key and vulnerable populations

Universal access to hepatitis C diagnosis and treatment will not be achieved unless services can be delivered to the populations that are most at risk for hepatitis C infection and yet often underserved. These include PWID, people in prisons, MSM, people with co-morbidities and other highly affected groups. These population groups are not only at higher risk of hepatitis C infection, but are also disproportionately affected by other communicable diseases, notably HIV. As mentioned in Chapter II, the coverage of harm reduction and prevention interventions, diagnosis and treatment among key populations remains low for both HCV and HIV, and the availability of disaggregated data is limited. A rights-based approach that provides non-discriminatory access to people-centred prevention and health-care services and engages affected populations in decision-making processes is critical to expanding outreach.

Similarly, injection and medical safety is vital for preventing transmission of HCV in health-care settings. Efforts also need to be maintained to ensure that the specific needs of other vulnerable groups, such as children and adolescents, or people with comorbidities such as those with HIV/HCV coinfection, are adequately addressed.

Key populations bear the highest burden but remain underserved

The Global Health Sector Strategy on Viral Hepatitis 2016–2021 highlights the importance of delivering harm reduction services to PWID, including access to sterile injecting equipment through needle and syringe programmes and drug dependence treatment such as opioid substitution therapy, alongside hepatitis C treatment and additional services such as for HIV and TB *(4)*. Yet, many national hepatitis elimination plans are yet to include comprehensive hepatitis C services for PWID and people in prisons. A WHO desk review in 2019 of 81 country hepatitis policies and plans for harm reduction and hepatitis C testing and treatment for these populations found that less than half outlined the necessary interventions for PWID in accordance with the Global Health Sector Strategy on Viral Hepatitis. As many as 30 plans did not reference PWID as a target population group for interventions at all. Interventions for people in prisons were similarly lacking – only 28 plans referenced interventions for this population group *(14)*. The main obstacles noted include lack of access to health insurance coverage by these groups, high costs of treatment, restrictive drug policies such as requirement for abstinence from drug use, and stigma and discrimination.

Another survey from 25 European countries in 2016–2017 among groups of patients with liver diseases gathered information on national policies related to harm reduction, screening/diagnosis and treatment for HCV in prison settings in the region. It found that 21 countries provide HCV screening/diagnosis in at least one prison; however, in most countries, this was not a standard policy and only offered on request. Twenty-one countries also provide HCV treatment in prisons, although coverage levels vary widely. Only two countries have needle and syringe programmes and 11 countries provide opioid substitution therapy in prisons in all parts of the country *(77)*.

Many countries are taking steps to address the barriers to access for key populations, supported by civil society organizations (Box 10) *(14)*. For example, in Ukraine, where the estimated prevalence of HCV infection is 55.9% among PWID, more than 200 000 patients are currently covered by a harm reduction programme run by the APH for the past 15 years across the country – one of the largest harm reduction programmes in the region *(78)*. The programme is funded by the Global Fund and other donors. The patients covered by the programme include the most vulnerable groups such as PWID, prison inmates and other key populations. The large-scale advocacy campaigns by APH, 100% Life, and other nongovernmental organizations from across the country played a key role in the development of Ukraine's national treatment programme in 2016 and the reduction in prices of DAAs.

In the Islamic Republic of Iran, which is estimated to have among the largest populations of PWID in the Middle East and North Africa region, a systematic review and meta-analysis found that the prevalence of HCV infection among this group ranges from 11.3% to 88.9%, and among the prison population, from 0.7% to 37.9% *(79)*. The national hepatitis control plan includes harm reduction interventions for these population groups and the coverage of these services is increasing. However, many PWID and people in prisons continue to face barriers to accessing these services, including due their lack of health insurance. While those with health insurance can access DAAs for US$ 81 per treatment course, those without health insurance face costs as high as US$ 670 per treatment course.

Australia, where more than half of the PWID are estimated to be HCV-infected, is adopting a simplified approach to service delivery for key populations *(80)*. An analysis of trends in HCV incident infection among PWID attending needle and syringe programmes in Australia from 1995 to 2010 found that a decline in HCV incidence coincided with considerable expansion of harm reduction programmes and a likely reduction in the number of PWID associated with significant changes in drug markets *(81)*. A survey among PWID who were enrolled in a community-based prospective observational study in Sydney found that community-based outreach was effective in engaging newly infected participants in monitoring and decision-making regarding treatment for hepatitis C. The factors that contributed to the acceptability of the outreach programme included privacy and discretion, building trust with non-judgemental staff, and ongoing, rather than one-off, post-test counselling sessions *(82)*.

In Portugal, the Group of Activists in Treatment (GAT) has been providing hepatitis diagnosis and treatment services to most affected populations such as PWID and people in prisons since 2010. The organization's four centres provide integrated interventions tailored to the needs of each community. For example, In-Mouraria, a drop-in centre for PWID, provides a standard prevention pack (clean injection, condoms); social services (information on HCV treatment, basic income and/or housing support); HCV, hepatitis B virus (HBV), HIV and syphilis rapid testing, and facilitates referral to care for people who test positive using peer supporters. The Government of Portugal is also working towards improved access to hepatitis C services in prison settings. Under a plan to eliminate hepatitis C in Portuguese prisons, 28 Portuguese hospitals and the General Directorate for Reintegration and Prison Services (under the Ministry of Justice) signed an agreement in 2018 to implement a new model of care for hepatitis C and HIV in prisons, relocating health professionals from hospitals to the prisons in order to provide critical on-site health care *(43)*.

There are also some examples of successful approaches to achieving HCV elimination among MSM. In the Netherlands, the majority of those diagnosed with acute HCV infection among people living with HIV are MSM. With a rapid uptake of DAAs since they became available in 2014, the Netherlands observed a 50% reduction by 2016 in acute HCV incidence among HIV-positive MSM. As of mid-2017, only 1.5% of the HIV-positive MSM remained HCV infected, making HCV elimination achievable in this group *(83)*.

Box 10
Civil society partners support access to hepatitis C services for key and vulnerable populations

A number of civil society organizations are playing a key role in supporting advocacy, policy development, service delivery and operations research to expand access to hepatitis C diagnostics and treatment, including for key populations.

The **World Hepatitis Alliance** works in partnership with over 290 member organizations across 94 countries to raise awareness on viral hepatitis, drive policy change, and promote access to services through running global public campaigns, convening high-level policy dialogue, and building local capacities. As the leading global patient organization for viral hepatitis, the Alliance played a key role in advocating to make the elimination of viral hepatitis by 2030 a global health priority. It is also driving a focus on "finding the missing millions" with a three-year campaign to promote a massive scale up in screening, diagnosis and linkage to care *(84)*.

Médecins Sans Frontières (MSF) has provided hepatitis C treatment to 30 000 patients in various countries *(85)*. In the city of Karachi, Pakistan, MSF supports a hepatitis C clinic that receives between 30 and 35 patients a day from vulnerable communities. At the end of 2019, nearly 2160 patients had been cured of hepatitis C since the project started in 2015. In Phnom Penh, Cambodia, MSF has supported hepatitis treatment with DAAs for more than 16 000 patients since the project started in 2016, using a simplified delivery model that has shifted certain tasks to nurses. Similar efforts have been supported in other regions, including in Kenya and Mozambique, with a focus on PWID. MSF also supports advocacy efforts to expand access to patented medicines.

Coalition PLUS supports advocacy and capacity-building efforts for local community-based organizations to engage people living with HIV and viral hepatitis in decision-making processes regarding programme design, implementation and evaluation, with a focus on those most affected. With support from Unitaid, Coalition PLUS has established partnerships with 15 local civil society organizations in seven countries – Brazil, Colombia, India, Indonesia, Malaysia, Morocco and Thailand – to engage in domestic policy dialogue and increase awareness on drug pricing and affordability. In India, for example, Coalition PLUS has worked with two local organizations to develop standard operating procedures for simplified case management, reach more PWID with testing and treatment and develop a free treatment programme for prisoners and indigent people. In Thailand, community-based organizations played a key role in addressing gaps in the national strategic plan and working with the MPP to extend voluntary licensing to daclatasvir *(86)*.

Médecins du Monde (MDM) supports advocacy efforts to address patent-related barriers, as well as the delivery of harm reduction programmes in collaboration with ministries of health in many countries. For example, in 2015–2016, MDM led efforts on patent opposition to sofosbuvir in Europe *(87)*. In Georgia, MDM piloted a peer-based model in Tbilisi in 2016 in collaboration with the national network of PWID. The programme integrated a proactive peer-based approach into a PWID community site, including raising awareness, providing free screening for viral hepatitis and HIV, and diagnostics for staging of liver disease. High levels of service uptake, adherence and retention were achieved throughout the cascade of care. Around 90% of clients missed none of the two-weekly medical appointments, and 98% of PWID completed treatment. Follow-up data 15 months after the end of treatment also demonstrated low rates of reinfection. This model is being rolled out on a national scale. In Viet Nam, MDM pioneered a similar peer-accompanied approach in Hanoi for PWID. In Myanmar, MDM recently initiated a new programme in collaboration with MSF to provide screening for HIV and HCV, harm reduction and treatment for 1400 PWID. MDM also supports advocacy efforts to address patent-related barriers to access in low- and middle-income countries *(88)*. In Kenya, through a collaboration with MSF, MDM integrated HCV treatment services within existing harm reduction programmes in Nairobi as a "one-stop shop" with strong outreach for service delivery *(43)*.

The **Treatment Action Group (TAG),** an independent community-based research and policy think tank, plays a major role at the global level in mobilizing civil society and communities to advocate for access to hepatitis C medicines at regional and country levels. TAG's HCV Project works in collaboration with affected communities, scientists, governments and manufacturers to track the pipeline for HCV innovations, increasing communities' diagnostics and treatment literacy, and providing technical assistance to build leadership capacity for advancing national elimination campaigns and amplifying community voices in planning and policy development. The HCV Project also advocates for harm reduction and drug decriminalization efforts.

Organizations such as the **Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS)** in France are supporting implementation science to improve the delivery of hepatitis care and treatment, in addition to their support for basic research. ANRS is supporting operations research in eight focus countries, including through modelling and impact studies, evaluation of the long-term impact of DAA treatment, and micro-elimination approaches.

Pregnant women, children, and adolescents

Globally, an estimated 3.5 (3.1–3.9) million children aged 0–19 years have chronic HCV infection *(89)*. Mother-to-child transmission is the most common cause of HCV infection in children, accounting for about 60% of new paediatric infections globally *(90)*. About 6–11% of children born to HCV-infected mothers acquire HCV, most of whom are infected near or at the time of birth. About 20% of infected children show spontaneous clearance, usually by 2 years of age; the remainder develop chronic infection.

Until early 2017, no DAA had been approved for use in children. In April 2017, the US FDA approved supplemental applications for sofosbuvir and a combination of sofosbuvir and ledipasvir to treat HCV infection in children 12–17 years, and there are now additional approvals for sofosbuvir/velpatasvir and glecaprevir/pibrentasvir *(91)*. Since then, sofosbuvir/ledipasvir has been approved for children 3 years of age and above, and sofosbuvir/velpatasvir for children 6 years of age and above, and similar approval is awaited for glecaprevir/pibrentasvir. The 2018 WHO guidelines *(12)* recommend that hepatitis C treatment be deferred until children reach 12 years, or until DAA regimens are approved for those less than 12 years. It is anticipated that these guidelines will be updated in 2020 to ensure uniform recommendations of DAA regimens in adults, adolescents and younger children. Phase III clinical trials are ongoing for the use of glecaprevir/pibrentasvir in children above 3 years of age. Data on the safety and efficacy of DAA treatment in pregnant women is still pending *(92)*.

Other vulnerable populations

Although data on the burden of HCV and service access among other vulnerable populations are limited overall, the available information suggests that groups such as migrant and refugee populations, and Indigenous Peoples, bear a disproportionate burden. A literature review of the data on HCV among immigrant populations found that immigrants and refugee populations from intermediate/high HCV-endemic countries to less- or non-endemic areas are more likely to have an increased risk of HCV infection, but face various barriers to accessing health-care services, such as patient–physician communication, language problems, beliefs such as in traditional medicine, ethnic disparities and inadequacies arising from socioeconomic problems, including lack of family support *(93)*.

A study on the socio-spatial distribution of HCV in Australia found that HCV notifications were seven times more likely to come from people residing in the poorest areas with high rates of reported non-employment and injecting drug use; and that notifications among Aboriginal and Torres Strait Islander people were around six times that of non-Indigenous people *(94)*. A large study spanning a 12-year period of data accrual on HCV among the Indigenous First Nations population in Canada found that infections occur in a significantly younger age group, and are more often in females and residents of urban communities as compared to the non-First Nations population. It also found that the burden of hepatitis C is increasing at a faster rate than in the non-First Nations population *(95)*.

A wider understanding of the various equity dimensions of access to hepatitis C diagnosis and treatment will be critical for countries to ensure that services can effectively reach the most affected populations, including in low-income and in middle- or high-income countries – leaving no one behind.

IV.5 Efficiency: Leveraging opportunities for procurement, financing and service delivery

Existing international procurement mechanisms can help to obtain cost-effective and timely products

As the demand and uptake of HCV diagnostics and treatment grows, there is an increasing need for efficient procurement and supply management mechanisms to ensure that products are available and accessible for all in need. A number of international procurement mechanisms are already supporting low- and middle-income countries to access HCV commodities at more affordable prices and these can be leveraged more systematically (Box 11). Some of these mechanisms use pooled procurement approaches, whereby several countries can jointly negotiate and obtain optimal volume-based prices.

Box 11
Support from international organizations for global health procurement *(31)*

UNDP manages one of the largest procurement operations of the UN and supports low- and middle-income countries to access life-saving medicines and other essential supplies. Under UNDP's quality assurance policy, procurement support can be provided for hepatitis C treatments that are WHO-prequalified, reviewed by the ERP, registered and marketed by stringent regulatory authorities, and/or meet standards through an in-house assessment of manufacturing sites and product dossiers if the above are not available. In 2018, the prices for DAAs obtained through UNDP procurement include sofosbuvir + daclatasvir at US$ 90, sofosbuvir/ledipasvir at US$ 90, and sofosbuvir/velpatasvir at US$ 270 per treatment course. UNDP is supporting the ministries of health in Azerbaijan, Kazakhstan, Turkmenistan and Ukraine to procure hepatitis C commodities for more than 25 000 patients, and plans to support more countries. UNDP also provides technical support on intellectual property, product regulations and supply chain strengthening.

The **Global Fund's Pooled Procurement Mechanism** (PPM) helps to aggregate order volumes for essential medicines across different countries and grant implementers to negotiate prices and delivery conditions with manufacturers who are either WHO prequalified or reviewed by the ERP. By doing so, the mechanism enables low- and middle-income countries to access competitive prices irrespective of the size of the market or volume of the order, and to eliminate procurement delays that may be caused by individual tendering processes. Leveraging its work on commodities for HIV, TB and malaria, the Global Fund's PPM has also supported the procurement of HCV medicines for some countries. The current prices negotiated by the mechanism per treatment course are US$ 94 for sofosbuvir + daclatasvir, US$ 79 for the fixed-dose combination of sofosbuvir/daclatasvir, and US$ 165 for sofosbuvir/ledipasvir.

The **Strategic Fund of the Pan American Health Organization** is a regional cooperation mechanism for pooled procurement of essential medicines and strategic health supplies. All products procured through the mechanism are prequalified by WHO, registered in the national regulatory authorities of reference medicines of the Region, or evaluated through internal processes for the assurance of quality. Hepatitis C medicines and are available through this Fund since 2017, and generic products since 2019. The prices negotiated by the Fund per treatment course are US$ 129 for sofosbuvir + daclatasvir, and US$ 4050 for sofosbuvir/velpatasvir or sofosbuvir/ledipasvir. WHO-prequalified HCV diagnostic tests can also be procured through the mechanism. As of June 2018, 33 countries in Latin America and the Caribbean had signed agreements with the Organization to use the mechanism; however, in practice, only those countries that are included in the voluntary licensing agreements of the originator companies can access the lower prices for HCV medicines.

Leveraging different financing options will be necessary for long-term sustainability

In order to achieve elimination, countries will need to leverage different financing options to ensure long-term sustainability of their efforts. This includes not only dedicated increases in domestic financing, but also efforts to build on existing international financing mechanisms to integrate hepatitis financing within broader universal health coverage plans. A number of countries such as Brazil, Egypt, Mongolia and Pakistan are already committing significant domestic resources to scale up HCV diagnosis and treatment. For example, in 2019, the Government of Pakistan announced a new national policy package to scale up prevention, testing and treatment in the country by 2030, and provide leadership and coordination to the provincial hepatitis programmes. An HCV transmission modelling exercise in Pakistan projected that the health system would recover the investment in elimination through savings in health-care costs due to prevented cases of cirrhosis and liver cancer in less than 3 years *(96)*.

WHO hosted a satellite meeting at the replenishment conference of the Global Fund in 2019 to consider strategies to optimize the use of global health resources for the hepatitis response in the context of universal health coverage *(97)*. At the event, partners emphasized the significant opportunity for an integrated approach. Recent analyses show that testing and treatment for HBV and HCV would represent a 0.5–1.5% increase in the price tag for universal health coverage at the current cost of commodities within an ambitious hepatitis elimination scenario by 2030, and a 1.5% increase in the price tag would lead to a 5% decrease in mortality and a 10% increase in healthy life years *(98)*.

Strategies such as optimizing procurement through existing mechanisms with economies of scale, leveraging existing international financing mechanisms such as the Global Fund and Unitaid (Boxes 12 and 13), and integrating with ongoing efforts (such as the use of POC testing that is already being funded for HIV and TB, or leveraging existing harm reduction programmes for HIV), could further drive down the price tag for the hepatitis response. At the satellite meeting, partners called for external catalytic funding from existing financing mechanisms for low- and middle-income countries to kick-start their elimination programmes, such as through the provision of seed funding for national situation analyses, planning and targeted start-up costs.

Box 12
Unitaid support for scaling up hepatitis C diagnosis and treatment

In 2015 and 2017, Unitaid's Executive Board passed resolutions to support the development of better diagnostic tools and expand access to diagnostics and treatment for HCV, including for people coinfected with HIV and HCV. With this commitment, Unitaid has invested more than US$ 50 million until 2020 to various projects. These will support national programmes to overcome barriers to accessing HCV products, and support innovators to develop new products. Funding has included support to FIND for market-shaping activities for novel diagnostics in collaboration with WHO, including a POC assay for HCV core antigen, hepatitis C self-testing, and a series of projects evaluating the impact of using GeneXpert for estimating HCV viral load and in promoting testing and treatment uptake in HIV clinics and harm reduction sites.

Similarly, through a grant to MSF, Unitaid has supported the development of simplified, adapted and affordable care models for HCV. A grant to Coalition PLUS is raising awareness of HCV among civil society organizations and national decision-makers *(99)*. Through a grant to the MPP, Unitaid supports access to HCV medicines through public health-oriented licensing, thus enabling generic companies to manufacture and supply quality-assured/ WHO-prequalified HCV medicines and combinations to low- and middle-income countries.

Box 13
Global Fund support for increasing access to harm reduction for people who inject drugs

In addition to the Global Fund's PPM support mentioned earlier, countries can also directly leverage opportunities for Global Fund grant financing to scale up integrated harm reduction programmes for PWID.

The Global Fund's *Technical Brief on harm reduction for people who use drugs* (2020) states that Global Fund resources can be used to increase HCV prevention, testing and management efforts, and support advocacy for treatment access and affordability, especially in settings where this provides a catalytic investment to support local regulations, registration and procurement *(100)*.

Specifically, countries with strong national or regional HCV epidemics among HIV-infected populations can consider including funding for HCV testing and treatment among HIV-infected persons within the Global Fund requests. This may be particularly relevant for countries with antiretroviral therapy (ART) cohorts constituted to an important extent by patients from key populations, notably MSM and PWID. Further, PWID are particularly concerned by HIV/HCV coinfection and harm reduction has a considerable prevention impact on HIV as well as on HCV. Global Fund policy also allows for the full harm reduction package to be included in funding requests, for improved access to harm reduction overall for the prevention of HIV and HCV transmission.

Countries that are interested in receiving HCV commodity support from the Global Fund can work through the Country Coordinating Mechanism (CCM) to allocate a budget in their HIV funding requests to the Global Fund. If the budget for HCV commodities does not fit within the Prioritized Funding Request allocation, it can be submitted as a Prioritized Above Allocation Request to be eligible for funding once additional resources become available on a rolling basis.[g]

Integrated service delivery models can promote efficiency

Integrated approaches to service delivery for hepatitis C – such as through integration with multidisease diagnostic platforms already in use for HIV and TB; building on HIV harm reduction and prevention programmes for key populations that are also highly affected by HCV; and leveraging cross-cutting opportunities for health system investments such as for data and surveillance systems, health worker capacity-building, procurement and supply management, and infection control in health-care settings – can lead to further efficiencies and ensure the delivery of people-centred services.

Many opportunities are currently being missed through fragmented disease-specific approaches, which do not support the wide-scale population scale up of testing and treatment. For example, although multidisease diagnostic platforms are available, these remain underutilized in many settings *(101)*. Approaches to deliver viral hepatitis prevention, testing and treatment interventions as part of services that are already reaching different communities and patient groups must be utilized optimally, such as HIV and TB treatment services, maternal and child health clinics, primary health care or harm reduction and drug dependence treatment services. Similarly, existing partnerships with communities affected by HIV and TB could also be leveraged to enhance programme design and delivery for communities affected by viral hepatitis. The WHO 2017 *Guidelines on testing and diagnosis of hepatitis B and C,* and the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection* recommend decentralized testing and treatment at primary health facilities or harm reduction sites, and integration of hepatitis C services with other services to increase their efficiency and reach.

In 2019, WHO collaborated with key partners to collate lessons learned from early experience in different aspects of the national hepatitis response to identify good practices from multiple settings that can guide other countries in scaling up their national response. The analysis identified good practices and lessons learned in seven key areas – community engagement and leadership; harm reduction among PWID; simplified service delivery; training of the health-care workforce; registration of medicines and diagnostics; forecasting and quantification for supply management; and optimizing procurement *(43)*. For example, in India, the state of Punjab is delivering decentralized care and treatment services to patients with chronic hepatitis C infection through a programme that is fully integrated into the existing public health system, leveraging existing clinicians, pharmacists and laboratories to do the needful. Medical specialists from 25 state government hospitals have been trained on the diagnosis and treatment of hepatitis C. Difficult cases are presented to and consulted with senior hepatologists from the Postgraduate Institute in Chandigarh using an online videoconferencing interface once every two weeks.

g Briefing notes on viral hepatitis C related activities to include in the Global Fund grant application 2020. The Global Fund, 2020. (Draft)

V Future priorities

Recent advances in the global landscape of hepatitis C diagnostics and treatments continue to provide a powerful momentum in low- and middle-income countries to scale up their public health response towards the elimination of viral hepatitis as a public health threat by 2030. This third global report highlights the latest developments in the key enablers of a successful response. These include access to diagnostics, norms and standards; national policy and regulatory environments; market conditions related to product availability, pricing and patents; and options for leveraging efficiencies in service delivery. The report also presents the impressive recent gains achieved by some high-burden countries towards universal access, and the diverse approaches used by them to overcome barriers in different contexts.

In countries that are leading the way, such as Egypt, Georgia, Mongolia, Pakistan and Rwanda, strong political commitment, wide access to testing, and a comprehensive government-led public health response have successfully leveraged domestic financing, seized available opportunities to address patent- and regulation-related barriers specific to the country context, and worked in collaboration with civil society to achieve price reductions for quality-assured products, and support access for those most at risk and vulnerable. These examples provide good practices for other low- and middle-income countries as they expand their response towards universal access.

The global response to viral hepatitis has a unique opportunity in 2020 to capitalize more extensively on this recent momentum to scale up and simplify access to high-impact interventions for hepatitis C. About 80% of people living with chronic hepatitis disease still do not have access to services. The progress achieved so far is uneven and fragmented, and the gains are fragile. Not all countries have been able to equally avail of opportunities to address barriers related to pricing, patents and product regulation; and the population groups who are most at risk continue to be underserved in access to services. In the context of the global COVID-19 pandemic, it is more critical than ever to ensure that the recent gains in the response to hepatitis C are not lost, and that efforts to scale up a public health response are sustained as part of broader efforts towards building sustainable and resilient health systems that can deliver universal health coverage.

Looking ahead, the following steps will be critical to accelerating a public health response and progressing towards the elimination targets by 2030.

Accelerating access to hepatitis C diagnostics. At the end of 2017, only 20% of people living with chronic HCV infection in low- and middle-income countries were aware of their status. As hepatitis C treatment becomes more affordable and widely available, the cost barriers shift to diagnostics. When large numbers of people need to be tested to identify each HCV-positive patient who needs treatment, it is urgent that the declines in treatment prices are accompanied by large-scale access to affordable diagnostics. Further simplification of service delivery through task-shifting at primary health facilities, the use of IVDs at or near the POC, and a differentiated care strategy with specialist referral as appropriate for those with complex problems, will also be critical to enabling more widespread access to screening and diagnosis.

Continued price reductions for more affordable hepatitis C diagnostics and treatment. The prices of hepatitis C diagnostics and treatment remain inaccessible for many, in particular, in upper-middle-income countries where generic competition is limited and an increasing proportion of poor and vulnerable populations live. Comprehensive strategies to obtain price reductions, including through addressing patent-related barriers and public health-oriented licensing, promoting competition among generic manufacturers of quality-assured products, price–volume negotiations with manufacturers, including value-for-money reagent rental agreements for HCV NAT platforms, promoting access to market intelligence and greater market transparency, and leveraging efficient procurement processes, will be key to ensuring that programmes are able to expand service availability.

Leaving no one behind. In 2018, less than 1% of PWID were living in countries with sufficient coverage of harm reduction services *(102)*. The global targets of hepatitis elimination by 2030 will not be met unless the needs are met of key, underserved and overlooked populations, including PWID, people in prisons, migrant and refugee populations, MSM and other vulnerable groups. A rights-based response that provides people-centred services through non-discriminatory access to health-care settings, will be critical to achieving true universal health coverage. Continuing to support local advocacy efforts by civil society organizations and communities, engaging communities in decision-making processes, and promoting community-led research and monitoring will further enhance the outreach and quality of programmes.

Facilitating product registration. Product registration with national regulatory authorities is necessary for a product to be sold in the country. Registration of as many manufacturers as possible can also increase competition, lower prices and minimize supply disruptions. Although product registrations are increasing, progress has been slow due to a number of factors, including requirements for generic manufacturers to provide locally obtained clinical trials data, even for WHO-prequalified products, low demand and uptake, and lack of information on opportunities to procure quality generic products. Mechanisms such as the use of the WHO Collaborative Registration Procedure can support countries in expediting product registration and expanding availability of proven DAA combinations.

Integrated approaches for greater domestic financing. Achieving long-term success will rely on increased domestic financing for high-impact interventions for viral hepatitis, integrated within broader financing packages for primary health care and universal health coverage across low-, middle- and high-income countries with diverse epidemics. Although international funding options for viral hepatitis are limited, it is also critical for national programmes to leverage other existing funding mechanisms, such as existing support from the Global Fund for harm reduction programmes or multidisease platforms/analysers. Improved costing and demand forecasts will also be important to secure resources, and to negotiate pricing agreements. Strong investment cases for hepatitis scale up and elimination have been developed in successful countries.

Leveraging synergies across the health sector. Integration of hepatitis testing, care and treatment with other services (e.g. HIV services) can greatly increase the efficiency and reach of hepatitis services and make universal access more affordable. For example, in 2017, WHO released guidance for countries to adopt multidisease diagnostic platforms/analysers, with the capability to use multiple disease-specific reagent sets on the same platform, including for HIV, viral hepatitis, chlamydia, gonorrhoea and TB *(103)*. Similarly, hepatitis C services can be delivered through existing harm reduction and HIV prevention programmes for key populations. Other cross-cutting opportunities, such as for surveillance systems and human resources, can also lead to further efficiencies.

© WHO/Conor Ashleig

Annexes

1. Drug profiles

2. Summary of the DAA procurement situation for hepatitis C treatment in selected low- and middle-income countries, 2019

3. Countries and areas not included in the voluntary licensing agreements

Annex 1: Drug profiles

1. Daclatasvir

General information

Product details

- Therapeutic class: NS5A inhibitor
- Originator company: BMS. The brand name of daclatasvir is Daklinza® *(104)*.
- First approved by the US FDA on 24 July 2015
- Tablet 30 mg, 60 mg (preferably scored)
- Indication: pangenotypic when used in combination with sofosbuvir
- Daclatasvir is part of the preferred pangenotypic regimens to be used in combination with sofosbuvir for the treatment of persons with chronic HCV infection aged 18 years and above, as given in the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (12)*.
- It is included in the twenty-first edition of the WHO *Model list of essential medicines,* 2019 *(39)*, and in the fourth Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team *(105)*.
- As of 2018, Optimus Pharma (India), Hetero (India), Cipla (India), Mesochem (China) and Laurus (India) manufacture the active pharmaceutical agent (API) and market it to finished product manufacturers.

Access, pricing and generic availability

Access programmes in low- and middle-income countries

In 2013, BMS signed a voluntary license agreement with the MPP, 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 *(106)*. As of mid-2020, there are seven generic companies with sublicensing agreements – Beximco, Cipla, Hetero, Laurus, Mylan, Natco and Zydus Cadila. BMS has tiered pricing in place.

In early 2020, BMS announced that the marketing authorizations for its originator product will be withdrawn or will be allowed to lapse in countries where the product is no longer routinely prescribed or where there are other therapeutic options available *(50)*. Following the withdrawal/lapse of the marketing authorization, the patents in those countries will also be allowed to lapse and will not be enforced in the interim period. This decision, which is effectively equivalent to a license expansion, has an important impact on access to daclatasvir. With this new policy, additional countries and areas, including some outside the licensed territory to the MPP, now have access to generic daclatasvir, with or without existing patents. These countries and areas are Albania, Armenia, Belarus, Bosnia, Bulgaria, Chile, Colombia, Egypt, Jordan, Kazakhstan, Kosovo,[h] Kyrgyzstan, Lebanon, North Macedonia, Malaysia, Mexico, Republic of Moldova, Montenegro, Peru, Romania, Serbia, Tajikistan, Thailand, Ukraine, Uruguay and the Bolivarian Republic of Venezuela *(22)*.

Generic production

Based on information collected through the WHO survey of manufacturers in 2019, the following companies are marketing generic daclatasvir: Beximo, Galenica, Getz, Hetero, Mylan, Pharco, Pharma 5, Zydus Cadila.

Prices reported by generic companies and by BMS, and additional information on prices reported by countries

The overall price of daclatasvir has continued to fall. Between 2016 and 2018, the lowest reported price of originator daclatasvir from BMS dropped from US$ 400 to US$ 182 per 28-day supply. The lowest reported price of generic daclatasvir dropped from US$ 15 to US$ 6 per 28-day supply over the same time period. The lowest generic price was found in the public sector in India, from Mylan. In Morocco, daclatasvir from a local manufacturer is available at US$ 154 per 28-day supply in the private sector. In China, originator daclatasvir is available for US$ 182 per 28-day supply. In contrast, in the Russian Federation, the price of originator daclatasvir is US$ 587 per 28-day supply from BMS.

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

Following the decision by BMS on the withdrawal/lapse of the marketing authorization, 26 additional countries and areas (Albania, Armenia, Belarus, Bosnia and Herzegovina, Bulgaria, Chile, Colombia, Egypt, Jordan, Kazakhstan, Kosovo,[h] Kyrgyzstan, Lebanon, North Macedonia, Malaysia, Mexico, Republic of Moldova, Montenegro, Peru, Romania, Serbia, Tajikistan, Thailand, Ukraine, Uruguay and the Bolivarian Republic of Venezuela) now have access to generic daclatasvir (with or without existing patents) *(22)*.

Between 2017 and 2019, the number of countries that had registered the originator source and generic sources of daclatasvir increased from 10 to 14 countries with originator sources, and from two to 16 countries with generic sources, respectively.

BMS daclatasvir was the first DAA to achieve WHO prequalification on October 2016. As of end 2020, there were WHO-prequalified generic sources of daclatasvir (Cipla, Hetero, Laurus, Mylan).

Patents

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

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	Lowest reported price 182 (details not available)			
Beximco Pharmaceuticals Ltd.	Beximco Pharmaceuticals Ltd.	Bangladesh	100	100		
Incepta Pharmaceuticals Ltd.	Incepta Pharmaceuticals Ltd.		140	140	140	
Galenica Pharmaceutical Laboratories	Galenica Pharmaceutical Laboratories	Morocco	150	150	270 or lower	270
Pharma 5	Pharma 5		143			
Pharco	Pharco	Egypt	6	6	12	12
Cipla	Cipla	India				
Laurus	Laurus		12–15*		12–15*	
Mylan Ltd	Mylan Ltd		5–7	15–18	Asia: 8–10 SSA:8–10	Asia:30–40 SSA: 20–25
Natco Pharma Ltd.	Natco Pharma Ltd.		61–70		70	
	Abbott India Ltd.		61			
Hetero Labs	Hetero Labs		12–15*	24	12–15*	24
Zydus Cadila	Zydus Cadila		5	10.5	30	30
Getz Pharma	Getz Pharma	Pakistan	36			

Notes:

1. **In bold:** WHO prequalified, ERP reviewed or approved by a stringent regulatory authority.
2. SSA: sub-Saharan Africa.
3. For Incepta Pharmaceuticals Ltd, Pharma 5 and Natco Pharma Ltd, prices reported are from the WHO 2018 edition of the report. No update was received for the 2020 edition.
4. **Source:* MPP licenses, July 2020.

Table A1.2: Regulatory approvals and filings by generic companies with WHO pre-qualified daclatasvir

	2016		2017		2019	
	Approvals	Filings	Approvals	Filings	Approvals	Filings
Cipla						
Hetero	2	0	8	41	10	31
Mylan						

h All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999)

2. Glecaprevir/pibrentasvir

Summary

- Therapeutic class: NS3/4A protease inhibitor + NS5A inhibitor
- Originator manufacturer: AbbVie. Brand name: Mavyret® (USA) *(107)*, Maviret® (EU)
- First approved by the US FDA on 3 August 2017
- Glecaprevir (100 mg)/pibrentasvir (40 mg) tablet
- Fixed-dose combination of glecaprevir, an NS3/4A protease inhibitor, and pibrentasvir, an NS5A inhibitor, is part of the preferred pangenotypic regimens to be used in the treatment of persons with chronic HCV infection aged 18 years and above, as given in the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (12)*.
- It is included in the twenty-first edition of the WHO *Model list of essential medicines*, 2019 *(39)*.
- It is not published in the Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team.
- Glecaprevir was developed by Enanta Pharmaceuticals. It was designed to enable once-daily dosing. Pibrentasvir was developed by AbbVie.
- At the end of 2018, originator company AbbVie signed a voluntary license agreement with the MPP to enable quality-assured generic manufacturers to develop and sell generic medicines containing glecaprevir/pibrentasvir in 96 low- and middle-income countries and areas. However, it does not include a number of upper-middle-income countries, or India.
- There is one generic sub-licensee for glecaprevir/pibrentasvir – Mylan, and production under this license is planned for the last quarter of 2020.
- For an overall patent situation, please refer to the MPP database, MedsPaL (http://www.medspal.org).

3. Sofosbuvir

General information

Product details

- Therapeutic class: nucleotide analogue inhibitor of NS5B polymerase
- Originator company: Gilead. Sofosbuvir brand name is Sovaldi® and Virunon® *(108)*.
- First approved by the US FDA on 6 December 2013, and by the EMA in January 2014.
- Sofosbuvir tablet, 400 mg
- Sofosbuvir is part of the preferred regimen for all genotypes in the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (12)*. It is included in the twenty-first edition of the WHO *Model list of essential medicines,* 2019 *(39)*, and in the fourth Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team.
- Sofosbuvir was developed in 1998 by Pharmasset, a biotechnological company founded by scientists from academic institutions, which Gilead acquired in November 2011.
- As of 2018, 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

Access programmes in low- and middle-income countries

Through the "Gilead Treatment Access Commitment" programme, the company offers expanded access to sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir through tiered pricing, generic licensing, registration and business partnerships, research, building country and NGO partnerships, and supporting domestic and international policy-making. A total of 105 countries are covered under the voluntary licensing territory. Gilead has also directly signed licensing agreements with generic suppliers for these products. As of end 2019, there were 14 generic suppliers that held a license for Gilead's products, one from Pakistan, two from Egypt and the rest from India: Aurobindo, Biocon, Cadila, Cipla, Ferozsons (Pakistan), Hetero, Laurus, Magic Pharma (Egypt), Mylan, Natco, Pharmed Healthcare (Egypt), Sequent, Strides and Sun Pharma *(31)*.

Generic production

Based on information collected through the WHO surveys of manufacturers in 2017 and 2019, the following companies are marketing generic sofosbuvir: Beacon, Beximco, Cipla, Galenica, Getz, Hetero, Incepta, Mylan, Natco, Pharco, Pharma 5, Richmond, Strides and Zydus Cadila.

Prices reported by generic companies and by Gilead, and additional information on prices reported by countries

Between 2016 and 2018, the lowest reported price of originator sofosbuvir from Gilead dropped from US$ 300 to US$ 230 per 28-day supply. The lowest reported price of generic sofosbuvir dropped from US$ 60 to US$ 15 per 28-day supply over the same time period. The lowest generic price was found in the public sector in India, from Mylan. In middle-income countries, Gilead reports that prices are negotiated country by country and are significantly discounted based on gross national income (GNI) per capita and disease burden.

Regulatory approvals and filings, and WHO prequalification approvals and submissions

Between 2017 and 2019, the number of countries that had registered the originator source and generic sources of sofosbuvir increased from 31 to 32 countries with originator sources, from 23 to 29 countries with generic sources, respectively.

As of end 2019, the originator product from Gilead and five generic products (from Cipla, Hetero, Mylan, Pharco and Strides) were WHO prequalified. Galenica indicated that it had plans to file.

As of mid-2020, registration had been done in 18 low- and middle-income countries in the Gilead voluntary licensing territory: Bolivia, Cameroon, Egypt, El Salvador, India, Indonesia, Kenya, Nigeria, Pakistan, Philippines, Rwanda, Thailand, Tunisia, Uganda, Ukraine, United Republic of Tanzania, Uzbekistan and Viet Nam.

Additional approvals were obtained in the following countries that were not included in the Gilead voluntary licensing territory: Argentina, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Georgia, Mexico, Peru, Uruguay and the Bolivarian Republic of Venezuela.

Patents

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

Table A3.1: Prices of sofosbuvir 400 mg, per 28-day supply, 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	Lower than private; exact price not reported	US$ 28 000	EU: Lower than private; exact price not reported	EU: 28 000
					MIC: Discounted pricing based on GNI per capita and disease burden; negotiated on country-by-country basis LIC: 230	
Laboratorios Richmond	Laboratorios Richmond	Argentina	350		LMIC: 350	
Beximco	Beximco	Bangladesh	86	86		
Incepta Pharmaceuticals Ltd.	Incepta Pharmaceuticals Ltd.		210	210	210	
Pharco	**Pharco**	Egypt	30	30	65–70	65–70
Cipla	**Cipla**	India				
Hetero Labs	**Hetero Labs**		20–22*	35	20–22*	35
Mylan Ltd	**Mylan Ltd**		14–16	30–40	Asia: 20–22* SSA: 14–16	Asia: 50–80 SSA: 20–25
Strides Shasun	**Strides Shasun**		20–22*	80	20–22*	
Zydus Cadila	Zydus Cadila		13	34	25	25
Galenica Pharmaceutical Laboratories	Galenica Pharmaceutical Laboratories	Morocco	Lower than private; exact price not reported	120	Lower than private; exact price not reported	120
Pharma 5	Pharma 5		274			
Getz Pharma	Getz Pharma	Pakistan	47.25			

Notes:

1. **In bold:** WHO prequalified, ERP reviewed or approved by a stringent regulatory authority.
2. LIC: low-income countries; LMIC: low- and middle-income countries; MIC: middle-income countries. EU: European Union; SSA: sub-Saharan Africa.
3. For Incepta Pharmaceuticals Ltd, Strides Shasun and Pharma 5, prices reported are from the WHO 2018 edition of the report. No update was received for the 2020 edition.
4. * *Source:* MPP licenses, July 2020

Table A3.2: Gilead regulatory approvals and filings for sofosbuvir in 2016 and 2017 *(109)*

	Approved LICs, LMICs, UMICs	Filed LICs, LMICs, UMICs	Approved territory	Filed territory
2016	20	14	9	8
2017	30	9	17	4
2019	29	1	18	1

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

Table A3.3: Regulatory approvals and filings by generic companies with WHO-prequalified sofosbuvir

	2016		2017		2019	
	Approvals	Filings	Approvals	Filings	Approvals	Filings
Cipla						
Hetero	6	20	19	32	33	20
Mylan						
Pharco			10	7	11	
Strides			13	16		

4. Sofosbuvir/daclatasvir

General information

Product details

- 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, tablet 400 mg/60 mg
- Sofosbuvir and daclatasvir are included in the twenty-first edition of the WHO *Model list of essential medicines,* 2019 *(39)* separately, but not under the epigraph "fixed-dose combinations". However, sofosbuvir/daclatasvir is listed as a fixed-dose combination in Invitations to submit an Expression of Interest for product evaluation to the WHO Prequalification Programme *(105)*.
- Sofosbuvir/daclatasvir is a recommended pangenotypic regimen for the treatment of persons with chronic HCV infection aged 18 years and above in the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (12)*.

Access, pricing and generic availability

Voluntary licensing and patents

Gilead has signed voluntary licensing agreements with 14 generic companies, which allows them to market and sell sofosbuvir in 105 countries. BMS signed a voluntary licensing agreement with the MPP, allowing generic companies to sell and market daclatasvir in 112 countries and any country where there is no patent in force, under the condition that they do not use BMS technology. Following the decision by BMS on the withdrawal/lapse of the marketing authorization in early 2020, an additional 26 countries also have access to generic daclatasvir (with or without existing patents) *(22)*.

Aurobindo, Cipla, Hetero, Laurus, Mylan and Natco have signed voluntary licensing 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 licensing 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 licensing agreement 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

Based on the information collected through the WHO survey of manufacturers in 2019, two generic manufacturers were producing the fixed-dose combination of sofosbuvir/daclatasvir – Galenica and Mylan. As of end 2020, a WHO-prequalified generic fixed-dose combination of sofosbuvir/daclatasvir was available from Mylan. Production from a generic manufacturer in Pakistan was also reported at a price of US$ 7 per 28-day supply in the public sector. Additional details were not available.

Table A4.1: Prices of sofosbuvir/daclatasvir 400 mg/60 mg, per 28-day supply, reported by companies and countries

Manufacturers	Marketing companies/ distributors	Country of origin	Local market prices		Export prices	
			Public (US$)	Private (US$)	Public (US$)	Private (US$)
Mylan Ltd	**Mylan Ltd**	India	23	45		
Galenica Pharmaceutical Laboratories	Galenica Pharmaceutical Laboratories	Morocco	330	330	330	330

Notes:

1. **In bold:** WHO prequalified, ERP reviewed or approved by a stringent regulatory authority.

5. Sofosbuvir/ledipasvir

General information

Product details

- Therapeutic class: nucleotide analogue inhibitor of an NS5B polymerase in combination with an NS5A inhibitor
- Sofosbuvir/ledipasvir, tablet 400 mg/90 mg
- Originator company: Gilead. Brand name is Harvoni® *(110)*.
- First approved by the US FDA on 10 October 2014. Approved by the EMA in November 2014
- Indication: treatment of chronic HCV infection with genotypes 1, 4, 5 and 6
- Sofosbuvir/ledipasvir is part of the preferred regimens in the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection* under the section treatment of genotypes 1, 4, 5 and 6 in adolescents aged 12–17 years *(12)*. It is included in the twenty-first edition of the WHO *Model list of essential medicines,* 2019 *(39)* and in the fourth Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team *(105)*.
- In 2017, Hetero (India), Mesochem (China), Xiamen Halosyntech (China) and Sequent (India) were among the manufacturers of ledipasvir's API, which they sell to finished product manufacturers.

Access, pricing and generic availability

Access programmes in low- and middle-income countries

Please refer to the sofosbuvir drug profile (Section 3 of this Annex) for a brief description of the Gilead access programme.

Generic production

Based on the information collected through the WHO survey of manufacturers in 2019, several generic companies produce a fixed-dose combination of sofosbuvir/ledipasvir *(see* Table A5.1). A WHO-prequalified generic fixed-dose combination was available from Mylan at as of end 2020. An ERP-reviewed combination was also available from Strides Shasun.

Prices reported by generic companies and by Gilead, and additional information on prices reported by countries

The lowest reported price of originator sofosbuvir/ledipasvir from Gilead dropped from US$ 400 to US$ 260 per 28-day supply between 2016 and 2017, and has remained unchanged since. The lowest reported price of the generic version dropped from US$ 250 to US$ 45 per 28-day supply over the same time period.

Table A5.1: 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	Lower than private; exact price not reported	31 500	EU: Lower than private; exact price not reported	EU: 14 040–19 500
					MIC: Discounted pricing based on GNI per capita and disease burden; negotiated on country-by-country basis LIC: 260	
Beximco	Beximco	Bangladesh	344	344		
Incepta Pharmaceuticals Ltd.	Incepta Pharmaceuticals Ltd.		350	350	350 Price reported in Uzbekistan: 157	
Hetero Labs	Hetero Labs	India	50	60	50	60
Mylan Ltd	**Mylan Ltd**		40–50	80–100	40–50	80–100
Strides Shasun	**Strides Shasun**		110	110	100	
Getz Pharma	Getz Pharma	Pakistan	233			

Notes:

1. **In bold:** WHO prequalified, ERP reviewed or approved by a stringent regulatory authority (Gilead Sciences, Hetero); or reviewed by the ERP (Mylan, Strides).
2. LIC: low-income countries; MIC: middle-income countries.
3. EU: European Union; GNI: gross national income.
4. For Incepta Pharmaceuticals Ltd and Strides Shasun, prices reported are from the WHO 2018 edition of the report. No update was received for the 2020 edition.

Regulatory approvals and filings, and WHO prequalification approvals and submissions

Between 2017 and 2019, the number of countries that had registered the originator source and generic sources of sofosbuvir/ledipasvir increased from 24 to 35 countries with originator sources, from five to 15 countries with generic sources, respectively.

As of June 2019, Gilead had obtained market authorization in 35 countries in its licensed territory, compared to three in 2016.

There were significantly more approvals and filings for sofosbuvir/ledipasvir in 2019 compared to 2017.

Two generic companies that market sofosbuvir/ledipasvir are ERP reviewed: Strides and Mylan.

Patents

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

Table A5.2: Gilead regulatory approvals and filings for sofosbuvir/ledipasvir in 2016, 2017 and 2019 *(111)*

	Approved LICs, LMICs, UMICs	Filed LICs, LMICs, UMICs	Approved territory	Filed territory
2016	9	11	3	11
2017	25	13	14	9
2019	35	2	22	1

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

6. Sofosbuvir/velpatasvir

General information

Product details

- Therapeutic class: fixed-dose combination of a nucleotide analogue inhibitor of NS5B polymerase (sofosbuvir) and an NS5A inhibitor (velpatasvir)
- Sofosbuvir/velpatasvir 400 mg/100 mg tablet
- Originator manufacturer: Gilead. The brand name of sofosbuvir/velpatasvir is Epclusa® *(112)*.
- First approved by the US FDA on 26 June 2016, and by the EMA on 28 July 2016.
- Sofosbuvir/velpatasvir is a recommended pangenotypic regimen for the treatment of persons with chronic HCV infection aged 18 years and above in the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (12)*. It is included in the twenty-first edition of the WHO *Model list of essential medicines,* 2019 *(39)* and was added to the fourth Invitation to submit an Expression of Interest for product evaluation to the WHO Prequalification Team *(105)*.
- In 2018, Mesochem (China), Hetero (India), Xiamen Halosyntech Co. Ltd (China) and Strides (India) manufactured the API (velpatasvir) and marketed it to finished product manufacturers.

Access, pricing and generic availability

Access programmes in low- and middle-income countries

Please refer to the sofosbuvir drug profile *(see Section 3 of this Annex)* for a brief description of the Gilead access programme. Gilead is yet to announce a price for countries in the voluntary licensing territory for sofosbuvir/velpatasvir.

Generic production

Based on the information collected through the WHO survey of manufacturers in 2019, the following companies are reported to be marketing sofosbuvir/velpatasvir: Beximco, Galenica, Getz, Hetero, Mylan, Pharma 5, Zydus Cadila.

Regulatory approvals and filings, and WHO prequalification approvals and submissions

Between 2017 and 2019, the number of countries that had registered the originator source and generic sources of sofosbuvir/velpatasvir increased from two to 23 countries with originator sources, and from one to six countries with generic sources, respectively.

One generic source of sofosbuvir/velpatasvir, from Mylan, was WHO-prequalified by end 2020.

Patents

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

Table A6.1: 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	Lower than private; exact price not reported	24 920	EU: Lower than private; exact price not reported	EU: 9 360–19 500
					MIC: Discounted pricing based on GNI per capita and disease burden; negotiated on country-by-country basis LIC: 300	
Beximco	Beximco	Bangladesh	276–344			
Hetero Labs	Hetero Labs	India		175		175
Mylan Ltd	**Mylan Ltd**		50–60	80–100	50–80	80–120
Strides Shasun	Strides Shasun		130	130	130	
Galenica Pharmaceutical Laboratories	Galenica Pharmaceutical Laboratories	Morocco	Lower than private; exact price not reported	385	Lower than private; exact price not reported	385
Getz Pharma	Getz Pharma	Pakistan	80			

Notes:

1. **In bold:** WHO prequalified, ERP reviewed or approved by a stringent regulatory authority.
2. LIC: low-income countries; LMIC: low- and middle-income countries; MIC: middle-income countries
3. EU: European Union
4. For Strides Shasun, prices reported are from the WHO 2018 edition of the report. No update was received for the 2020 edition.

7. Sofosbuvir/velpatasvir/voxilaprevir

Summary

- Therapeutic class: fixed-dose combination of sofosbuvir, a nucleotide analogue NS5B polymerase inhibitor; velpatasvir, an NS5A inhibitor; and voxilaprevir, an NS3/4A protease inhibitor
- Originator manufacturer: Gilead. The brand name is Vosevi® *(113)*.
- Approved by the US FDA on 18 July 2017 and by the EMA on 28 July 2017
- Sofosbuvir/velpatasvir/voxilaprevir is a recommended regimen in the WHO 2018 *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection* for the retreatment of HCV-infected persons who previously failed a DAA regimen *(12)*. It is not included in the twenty-first edition of the WHO *Model list of essential medicines*, 2019 *(39)* and not published in the Invitation to submit an Expression of Interest to the WHO Prequalification Team for product evaluation.
- Sofosbuvir/velpatasvir/voxilaprevir is included in the licensing agreement by Gilead for generic suppliers.
- As of mid-2020, sofosbuvir/velpatasvir/voxilaprevir was registered in two low- and middle-income countries (Argentina and the Dominican Republic) and dossiers were filed in four low- and middle-income countries (Brazil, Chile, Colombia and Egypt) *(114)*.
- There are no generic versions.
- For an overall patent situation, please refer to the MPP database, MedsPaL (http://www.medspal.org).

Table A7.1: Prices of sofosbuvir/velpatasvir/voxilaprevir 400 mg/100 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	Lower than private; exact price not reported	24 920	EU: Lower than private; exact price not reported	EU: 14 040–21 195
					MIC: Discounted pricing based on GNI per capita and disease burden; negotiated on country-by-country basis LIC: Also negotiated on a country-by-country basis	

Notes:

1. LIC: low-income countries; LMIC: low- and middle-income countries; MIC: middle-income countries
2. EU: European Union; GNI: gross national income

Annex 2: Summary of the DAA procurement situation in selected low- and middle-income countries with a high burden of hepatitis C, 2019

	Registered DAAs	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Inclusion in licensing agreements for DAAs: • Gilead licensing agreement for SOF, SOF/LDV, SOF/VEL • BMS and MPP licensing agreement, or patent withdrawal/lapse for DCV • AbbVie and MPP licensing agreement for G/P	Compulsory licensing (CL)/ government use	Generic local production
WHO African Region						
Rwanda	DCV BMS	(donation in 2018)		SOF SOF/LDV SOF/VEL DCV G/P	No	No
	SOF Gilead	230				
	SOF/LDV Gilead	260				
	SOF/VEL Gilead					
	SOF/VEL/VOX Gilead					
	DCV generic					
	SOF generic					
	SOF + DCV generic	20				
	SOF/LDV generic					
WHO Region of the Americas						
Brazil	DCV BMS	686		None	No	No (planned)
	G/P AbbVie	2432				
	SOF Gilead					
	SOF Blanver	235				
	SOF/LDV Gilead	383				
	SOF/VEL Gilead	490				

	Registered DAAs	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Inclusion in licensing agreements for DAAs: • Gilead licensing agreement for SOF, SOF/LDV, SOF/VEL • BMS and MPP licensing agreement, or patent withdrawal/lapse for DCV • AbbVie and MPP licensing agreement for G/P	Compulsory licensing (CL)/ government use	Generic local production
WHO Eastern Mediterranean Region						
Egypt	DCV BMS			SOF SOF/LDV SOF/VEL DCV G/P	No	Yes
	SOF Gilead					
	SOF/LDV Gilead					
	SOF/VEL Gilead					
	SOF/VEL/VOX Gilead					
	DCV Pharco and 4 companies	6	6			
	SOF Pharco and 17 companies		30			
	SOF/DCV FDC generic	16				
	SOF/LDV generic					
	SOF/VEL generic					
Morocco	DCV Galenica, Pharma 5		150	SOF SOF/LDV SOF/VEL DCV G/P	No	Yes
	SOF Galenica, Pharma 5		120			
	SOF/DCV Galenica	330	330			
	SOF/VEL Gilead					
	SOF/LDV Gilead	441				
Pakistan	SOF/DCV Getz, Searle and GSK	7–10		SOF SOF/LDV SOF/VEL DCV G/P	No	Yes
	SOF/VEL generic	52				
WHO European Region						
Georgia	SOF Gilead	Donation		DCV G/P	No	No
	SOF/LDV Gilead	Donation				
	SOF/VEL Gilead	Donation				
Russian Federation	DCV BMS	587		None	No	No
	G/P AbbVie	2668				
	SOF Gilead	1099				
	SOF/VEL Gilead					
	SOF/LDV Gilead					
Ukraine	SOF Gilead			SOF SOF/LDV SOF/VEL DCV	No	No
	SOF/LDV Gilead					
	SOF/VEL Gilead					
	SOF + DCV Mylan	30				
	SOF + DCV Strides					
	SOF/LDV Mylan	34				
	SOF/VEL Mylan	100				

	Registered DAAs	Price, public sector, per 28-day supply (in US$)	Price, private sector, per 28-day supply (in US$)	Inclusion in licensing agreements for DAAs: • Gilead licensing agreement for SOF, SOF/LDV, SOF/VEL • BMS and MPP licensing agreement, or patent withdrawal/lapse for DCV • AbbVie and MPP licensing agreement for G/P	Compulsory licensing (CL)/ government use	Generic local production
WHO South-East Asia Region						
India	DCV Mylan	6	16.5	SOF SOF/LDV SOF/VEL DCV	No	Yes
	SOF Mylan, Hetero	15	35			
	SOF/LDV Mylan, Hetero	45	60			
	SOF/VEL Mylan	55	90			
	SOF/DCV Mylan	23	45			
	SOF/DCV multiple suppliers	39				
WHO Western Pacific Region						
China	DCV (BMS): June 2017	182		No	No	Yes Local production of other DAAs
	SOF (Gilead): Sep 2017	2747				
	G/P AbbVie – under examination					
	SOF/LDV Gilead (2017 Phase III)					
	SOF/VEL/VOX Gilead (2017 Phase III)					
Malaysia	DCV BMS			SOF SOF/LDV SOF/VEL DCV	Yes for SOF	No
	DCV Pharco	41–63				
	SOF Gilead					
	SOF Pharco	34				
	SOF/VEL Gilead					
	G/P AbbVie					
	SOF Strides					
	SOF Hetero					
	SOF Natco					
	SOF Strides					
	SOF/VEL Mylan					
Mongolia	DCV Mylan	36		SOF SOF/LDV SOF/VEL DCV	No	No
	SOF Hetero, Natco, Strides, Mylan	80–91				
	SOF/LDV Hetero, Natco, Mylan, Strides	80				
	SOF/LDV Gilead	267				

BMS: Bristol-Myers Squibb; DAA: direct-acting antiviral; DCV: daclatasvir; G/P: glecaprevir/pibrentasvir; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

Source: Report of the WHO survey on access to DAAs, 2019 and MPP *(22)*.

Annex 3: Lower-middle and upper-middle-income countries and areas not included in at least one voluntary licensing agreement, 2020

The following tables provide information on the countries and areas that are not included in at least one voluntary license agreement of the three originator manufacturers of DAAs:

- **Gilead voluntary licensing agreement** for sofosbuvir, sofosbuvir/velpatasvir, sofosbuvir/ledipasvir and sofosbuvir/velpatasvir/voxilaprevir;
- **BMS and MPP voluntary licensing agreement** for daclatasvir; or patent withdrawal/lapse following the announcement in 2020 that the marketing authorizations for its originator product will be withdrawn or will be allowed to lapse in countries and areas where the product is no longer routinely prescribed or where there are other therapeutic options available;
- **AbbVie and MPP voluntary licensing agreement** for glecaprevir/pibrentasvir.

Countries in **bold** are among the 20 countries and areas with the highest burden of HCV infection globally, based on estimates from 2017.

Region of the Americas				
	Income category	**BMS VL or patent withdrawal/lapse**	**Gilead VL**	**AbbVie VL**
Argentina	UMIC	NO	NO	NO
Belize	UMIC	YES	NO	YES
Brazil	UMIC	NO	NO	NO
Colombia	UMIC	YES	NO	NO
Costa Rica	UMIC	YES	NO	NO
Dominican Republic	UMIC	YES	NO	NO
Ecuador	UMIC	YES	NO	NO
El Salvador	LMIC	YES	YES	NO
Grenada	UMIC	YES	NO	YES
Guatemala	UMIC	YES	YES	NO
Honduras	LMIC	YES	YES	NO
Jamaica	UMIC	YES	NO	NO
Mexico	UMIC	YES	NO	NO
Panama	UMIC	YES	NO	NO
Paraguay	UMIC	YES	YES	NO
Peru	UMIC	YES	NO	NO
Saint Lucia	UMIC	YES	NO	YES
Saint Vincent and the Grenadines	UMIC	YES	YES	NO
Venezuela (Bolivarian Republic of)	UMIC	YES	NO	NO

African Region				
	Income category	**BMS VL or patent withdrawal/lapse**	**Gilead VL**	**AbbVie VL**
Algeria	UMIC	YES	YES	NO

Eastern Mediterranean Region				
	Income category	**BMS VL or patent withdrawal/lapse**	**Gilead VL**	**AbbVie VL**
Iran (Islamic Republic of)	UMIC	NO	NO	NO
Iraq	UMIC	YES	NO	NO
Jordan	UMIC	YES	NO	YES
Lebanon	UMIC	YES	NO	NO
Syrian Arab Republic	LMIC	YES	NO	NO
Yemen	LMIC	YES	NO	YES

European Region				
	Income category	**BMS VL or patent withdrawal/lapse**	**Gilead VL**	**AbbVie VL**
Azerbaijan	UMIC	YES	NO	NO
Belarus	UMIC	YES	YES	NO
Albania	UMIC	YES	NO	NO
Armenia	LMIC	YES	NO	NO
Bosnia and Herzegovina	UMIC	YES	NO	NO
Bulgaria	UMIC	YES	NO	NO
Croatia	UMIC	NO	NO	NO
Georgia	LMIC	YES	NO	YES
Kazakhstan	UMIC	YES	NO	NO
Kosovo*	LMIC	YES	NO	NO
Kyrgyzstan	LMIC	YES	YES	NO
Montenegro	UMIC	YES	NO	NO
Republic of Moldova	LMIC	YES	NO	NO
Romania	UMIC	YES	NO	NO
Russian Federation	UMIC	NO**	NO	NO
Serbia	UMIC	YES	NO	NO
Tajikistan	LMIC	YES	YES	NO
North Macedonia	UMIC	YES	NO	NO
Turkey	UMIC	NO	NO	NO
Ukraine	LMIC	YES	YES	NO

* All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999)

** The Russian Federation has an exclusive license from BMS under which generic production is possible.

South-East Asia Region				
	Income category	**BMS VL or patent withdrawal/ lapse**	**Gilead VL**	**AbbVie VL**
India	LMIC	YES	YES	NO
Thailand	UMIC	YES	YES	NO

Western Pacific Region				
	Income category	**BMS VL or patent withdrawal/ lapse**	**Gilead VL**	**AbbVie VL**
China	UMIC	NO	NO	NO
Malaysia	UMIC	YES	YES	NO
Mongolia	LMIC	YES	YES	NO

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

References

1. Global hepatitis report. 2017. Geneva: WHO; 2017 (https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/, accessed 20 May 2020).
2. Coronavirus disease (COVID)-19: weekly epidemiological update – 3 November 2020. In: World Health Organization [website] (https://www.who.int/publications/m/item/weekly-epidemiological-update---3-november-2020, accessed 6 November 2020).
3. Results report 2020. Geneva: The Global Fund; September 2020 (https://www.theglobalfund.org/media/10103/corporate_2020resultsreport_report_en.pdf?u=637356227598900000, accessed 22 Sep 2020).
4. Global health sector strategy on viral hepatitis 2016–2021. Geneva: WHO; 2016 (https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/, accessed 20 May 2020).
5. Hepatitis C fact sheet. Geneva: WHO; 2019 (https://www.who.int/news-room/fact-sheets/detail/hepatitis-b, accessed 16 June 2020).
6. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multi-stage systematic review. Lancet Glob Health. 2017;5(12): E1192-E1207 (https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(17)30375-3/fulltext, accessed 22 June 2020).
7. Trickey A, Fraser H, Lim AG, Peacock A, Colledge S, Walker JG et al. The contribution of injection drug use to hepatitis C virus transmission globally, regionally and at country level: a modelling study. Lancet Gastroenterol Hepatol. 2019;4:435–44 (https://www.thelancet.com/pdfs/journals/langas/PIIS2468-1253(19)30085-8.pdf, accessed 27 May 2020).
8. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGown C et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis. 2016;16(7):797–808. (https://pubmed.ncbi.nlm.nih.gov/26922272/, accessed 16 June 2020).
9. Jin F, Dore GJ, Matthews G, Luhmann N, Macdonald V, Bajis S et al. A systematic review and meta-analysis of the prevalence and incidence of hepatitis C virus infection in men who have sex with men. Lancet Gastroenterol Hepatol. Published online 17 November 2020; http://doi.org/10.1016/5246B-1253(20)30303–4.
10. Global report on access to hepatitis C treatment: focus on overcoming barriers. Geneva: WHO; October 2016 (https://www.who.int/hepatitis/publications/hep-c-access-report/en/, accessed 7 September 2020).
11. Guidelines on hepatitis B and C testing. 2017. Geneva: WHO; 2017 (https://www.who.int/hepatitis/publications/guidelines-hepatitis-c-b-testing/en/, accessed 3 August 2020).
12. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection. Geneva: WHO; 2018 (https://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2018/en/, accessed 21 May 2020).
13. Consolidated strategic information guidelines for viral hepatitis: planning and tracking progress towards elimination. Geneva: WHO; 2019 (https://www.who.int/hepatitis/publications/strategic-information-hepatitis/en/, accessed 29 June 2020).
14. Access to hepatitis C testing and treatment for people who inject drugs and people in prisons – a global perspective. Policy brief. Geneva: WHO; 2019 (https://www.who.int/hepatitis/publications/idu-prison-access-hepatitis-c/en/, accessed 20 May 2020).
15. Lazarus J, Safreed-Harmon K, Thursz MR, Dillon JF, El-Sayed MH, Elsharkawy AM et al. The micro-elimination approach to eliminating hepatitis C: strategic and operational considerations. Review. Semin Liver Dis. 2018;38(3):181–92. doi: 10.1055/s-0038-1666841. Epub 2018 Jul 9. (https://pubmed.ncbi.nlm.nih.gov/29986353/?from_term=micro-elimination&from_pos=1, accessed 20 May 2020).
16. Kracht PAM, Arends JE, van Erpecum KJ, Urbanus A, Willemse JA, Hoepelman AIM et al. Strategies for achieving viral hepatitis C micro-elimination in the Netherlands. Hepatol Med Policy. 2018;3:12 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6162944/, accessed 20 May 2020).
17. Godin A, Kronfli N, Cox J, Alary M, Maheu-Giroux M. The role of prison-based interventions for hepatitis C virus (HCV) micro-elimination among people who inject drugs in Montreal, Canada. Int J Drug Policy. 2020;102378 (https://pubmed.ncbi.nlm.nih.gov/32278651/?from_term=micro-elimination&from_page=3&from_pos=7, accessed 20 May 2020).
18. Shiha G, Soliman R, Mikhail NNH, Easterbrook P. An educate, test and treat model towards elimination of hepatitis C infection in Egypt: feasibility and effectiveness in 73 villages. J Hepatol. 2020;72(4):658–69 (https://pubmed.ncbi.nlm.nih.gov/31734097/, accessed 16 June 2020).
19. Feld J. HCV elimination: it will take a village and then some. Editorial. J Hepatol. 2020;72(4):P601–3 (https://www.journal-of-hepatology.eu/article/S0168-8278(20)30002-7/fulltext, accessed 16 September 2020).
20. Punjab seeks WHO help to fight hepatitis C. In: Hep Voices [website], February 2020 (https://hepvoices.org/2020/02/punjab-seeks-who-help-to-fight-hepatitis-c/, accessed 22 June 2020).
21. WHO welcomes Egypt's support to 14 African countries in their fight against hepatitis C. Geneva: WHO Regional Office for the Eastern Mediterranean; 2019 (http://www.emro.who.int/media/news/who-welcomes-egypts-support-to-14-african-countries-in-their-fight-against-hepatitis-c.html, accessed 20 May 2020).

22. Affordable versions of hepatitis C medicine daclatasvir soon available in additional countries. Press Release, 16 March 2020. In: Medicines Patent Pool [website] (https://medicinespatentpool.org/news-publications-post/affordable-versions-of-hepatitis-c-medicine-daclatasvir-soon-available-in-additional-countries/, accessed 18 September 2020).

23. The Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) project. In: FIND [project webpage] (https://www.finddx.org/hcv-hiv/head-start/, accessed 3 August 2020).

24. Benzaken AS, Girade R, Catapan E, Pereira GFM, de Almeida EC, Vivaldini S et al. Hepatitis C disease burden and strategies for elimination by 2030 in Brazil. A mathematical modeling approach. Braz J Infect Dis. 2019:23(3):182–90 (https://www.sciencedirect.com/science/article/pii/S1413867019301278?via%3Dihub, accessed 25 September 2020).

25. Da Fonseca EM, Shadlen K, Bastos FI. Brazil's fight against hepatitis C – universalism, local production, and patents. N Engl J Med. 2019;380(7):605–7. (https://www.nejm.org/doi/full/10.1056/NEJMp1812959, accessed 27 May 2020).

26. Polaris Observatory [online database] (https://cdafound.org/polaris/, accessed 20 May 2020).

27. Waked I, Esmat G, Elsharkawy A, El-Serafy M, Abdel-Razek W, Ghalab R et al. Screening and treatment program to eliminate hepatitis C in Egypt. N Engl J Med. 2020;382;12 (https://www.nejm.org/doi/pdf/10.1056/NEJMsr1912628, accessed 17 October 2020).

28. Hagan ML, Kasradze A, Slayer SJ, Gamkrelidze A, Alkhazashvili M, Chanturia G et al. Hepatitis C prevalence and risk factors in Georgia, 2015: setting a baseline for elimination. BMC Public Health. 2019;19 (Suppl 3):480 (https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-6784-3, accessed 12 October 2020).

29. Schroeder SE, Pedrana A, Scott N, Wilson D, Kuschel C, Aufegger L et al. Innovative strategies for the elimination of viral hepatitis at a national level; a country case series. Liver Int. 2019;39:1818–36.

30. Compendium of good practices in the health sector response to viral hepatitis in the WHO European Region. Copenhagen: WHO Regional Office for Europe; 2020 (https://www.euro.who.int/en/health-topics/communicable-diseases/hepatitis/publications/2020/compendium-of-good-practices-in-the-health-sector-response-to-viral-hepatitis-in-the-who-european-region-2020, accessed 12 October 2020).

31. Hepatitis C Market Report. Issue 1. Clinton Health Access Initiative; May 2020 (https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2020/05/Hepatitis-C-Market-Report_Issue-1_Web.pdf, accessed 28 May 2020).

32. Urgent increase in hepatitis testing and treatment needed: Mongolia showcases impressive progress, inspiring hope and opportunities. Geneva: WHO; 2018 (https://www.who.int/hepatitis/news-events/hepatitis-testing-treatment-increase/en/, accessed 21 May 2020).

33. 15 million people affected with hepatitis B and C in Pakistan: Government announces ambitious plan to elimimate hepatitis. In: World Health Organization: Hepatitis [website]. 2019 (https://www.who.int/hepatitis/news-events/pakistan-hepatitis-elimination-plan/en/, accessed 21 May 2020).

34. Pakistan's investment in hepatitis may see return within years. In: World Health Organization: Hepatitis [website]. 2018 (https://www.who.int/hepatitis/news-events/towards-hepatitis-elimination-pakistan/en/, accessed 21 May 2020).

35. [Pharmstandard and Bristol-Myers Squibb (BMS) signed an agreement to transfer rights to Ducklin's drug for the treatment of chronic hepatitis C]. In: Pharmstandard [website]. 30 October 2019 (https://pharmstd.ru/archivedetails_64_2918.html, accessed 17 October 2020). [In Russian]

36. Cheshnokova O. [FAS insisted on compulsory licensing of drugs]. In: Vademecum [website] (https://vademec.ru/news/2016/09/07/fas-nastaivaet-na-prinuditelnom-litsenzirovanii-lekarstv/, accessed 17 October 2020). [In Russian]

37. [Report: procurement of drugs for the treatment of hepatitis C in the Russian Federation for 2019–2020]. In: IPTCru [website] (https://itpcru.org/2020/07/27/otchet-zakupki-preparatov-dlya-lecheniya-gepatita-s-v-rf-za-2019-2020-gg/, accessed 17 October 2020). [In Russian]

38. Grebely J, Lamoury FMJ, Hajarizadeh B, Mowat Y, Marshall AD, Bajis S et al. Evaluation of the Xpert HCV viral load point-of-care assay from venepuncture-collected and finger-stick capillary whole-blood samples: a cohort study. Lancet Gastroenterol Hepatol. 2017;2(7):514–20 (https://www.sciencedirect.com/science/article/abs/pii/S2468125317300754, accessed 5 October 2020)

39. WHO Model List of Essential Medicines, 21st List. Geneva: WHO; 2019 (https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1, accessed 17 October 2020).

40. FPPs under assessment. In: World Health Organization: Essential Medicines and Health Products [website] WHO (https://extranet.who.int/prequal/content/dossier-status, accessed 9 June 2020).

41. Medicines/Finished pharmaceutical products. In: World Health Organization: Essential Medicines and Health Products [website] (https://extranet.who.int/prequal/content/prequalified-lists/medicines, accessed 9 June 2020).

42. Implementation of daclatasvir licenses: development report 2017–March 2020. Medicines Patent Pool; 2020 (https://medicinespatentpool.org/uploads/2020/07/MPP_DAC_licence_implementation_update_July_2020.pdf, accessed 22 Sep 2020).

43. Seven good practices and lessons learned in the global viral hepatitis response. European Association for the Study of the Liver (EASL) Conference 2019 Brief, WHO-EASL Special Symposium on Good practices and lessons learned from global viral hepatitis scale-up, 13 April 2019 (https://program.m-anage.com/ilc2019/en-GB/ProgramSearch/Program/?searchstring=&programid=63048&pProgramGrade=Scientific&pHideLogin=False, accessed 5 November 2020).

44. [4 years of sofosbuvir in Russia: an assessment of availability, a look into the future and whether it is worth issuing a compulsory license]. In: ITPCru [website]. 2020 (https://itpcru.org/2020/03/25/4-goda-sofosbuvira-v-rossii-oczenka-dostupnosti-vzglyad-v-budushhee-i-stoit-li-vydavat-prinuditelnuyu-liczenziyu/, accessed 17 October 2020). [In Russian]

45. Patent for sofosbuvir extended in Russia. In: Rouse [website]. 27 April 2020 (https://www.rouse.com/magazine/news/patent-for-sofosbuvir-extended-in-russia/?tag=russia, accessed 17 October 2020).

46. China patent challenge compels Gilead to withdraw key patent claims on sofosbuvir base compound, opening life-saving hepatitis C treatment access for millions. Press release. In: I-MAK [website]. 9 August 2018 (https://www.i-mak.org/2018/08/09/china-patent-challenge-compels-gilead-withdraw-key-patent-claims-sofosbuvir-base-compound-opening-life-saving-hepatitis-c-treatment-access-millions/, accessed 17 October 2020).

47. MedsPaL. Sofosbuvir China. In: Medicines Patent Pool [website] (https://www.medspal.org/?keywords=sofosbuvir+china&page=1, accessed 9 June 2020).

48. Licenses. In: Medicines Patent Pool [website] (https://medicinespatentpool.org/what-we-do/global-licence-overview/, accessed 13 July 2020).

49. Access to Medicines Tracker. In: Medicines Patent Pool [website] (https://medicinespatentpool.org/progress-achievements/access-to-medicines-tracker/, accessed 13 July 2020).

50. Important information about the discontinuation of Daklinza. In: Bristol-Myers Squibb [website] (https://www.bms.com/patient-and-caregivers/our-medicines/discontinuation-of-daklinza.html, accessed 16 June 2020).

51. MedsPal – The Medicines Patent and Licences Database. In: Medicines Patent Pool [website] (https://www.medspal.org/?page=1, accessed 25 May 2020).

52. Moon S, Erickson E. Universal medicine access through lump-sum remuneration – Australia's approach to hepatitis C. N Engl J Med. 2019;380:607–10.

53. Gee R. Louisiana's journey toward eliminating hepatitis C. Health Affairs Blog. 1 April 2019 (https://www.healthaffairs.org/do/10.1377/hblog20190327.603623/full/, accessed 17 October 2020).

54. Gilead Sciences. Louisiana launches hepatitis C innovative payment model with Asegua Therapeutics, aiming to eliminate the disease. Press release. 26 June 2019 (https://www.gilead.com/news-and-press/press-room/press-releases/2019/6/louisiana-launches-hepatitis-c-innovative-payment-model-with-asegua-therapeutics-aiming-to-eliminate-the-disease, accessed 18 October 2020).

55. HCA issues request for proposals from drug manufacturers for hepatitis C treatment and services. 23 January 2019 (https://www.hca.wa.gov/about-hca/hca-issues-request-proposals-drug-manufacturers-hepatitis-c-treatment-and-services, accessed 17 October 2020).

56. Health Care Authority announces AbbVie US LLC as apparently successful bidder for hepatitis C virus treatment drug. In: Washington State Health Care Authority [website]. 26 April 2019 (https://www.hca.wa.gov/about-hca/health-care-authority-announces-abbvie-us-llc-apparently-successful-bidder-hepatitis-c, accessed 17 October 2020).

57. HCA finalizes contract with AbbVie to eliminate HCV in Washington State. In: Washington State Health Care Authority [website]. 1 July 2019 (https://www.hca.wa.gov/about-hca/hca-finalizes-contract-abbvie-eliminate-hcv-washington-state, accessed 17 October 2020).

58. Dunn A. AbbVie wins hep C contract with Washington state in latest 'Netflix' deal. In: Biopharma Dive [website]. 27 April 2019 (https://www.biopharmadive.com/news/abbvie-wins-hep-c-contract-with-washington-state/553576/, accessed 17 October 2020).

59. NHS England strikes world leading deal to help eliminate hepatitis C. In: NHS England [website]. 30 April 2019 (https://www.england.nhs.uk/2019/04/nhs-england-strikes-world-leading-deal-to-help-eliminate-hepatitis-c/, accessed 17 October 2020).

60. Hawkes N. NHS England finalises procurement to eliminate hepatitis C. BMJ. 2019;365:1994 (https://pubmed.ncbi.nlm.nih.gov/31043369/, accessed 17 October 2020).

61. Maistat L, Kravchenko N, Reddy A. Hepatitis C in eastern Europe and Central Asia: a survey of epidemiology, treatment access and civil society activity in eleven countries. Hepatol Med Policy. 2017;2:9. DOI:10.1186/s41124-017-0026-z

62. Promoting access to medical technologies and innovation – intersections between public health, intellectual property and trade, second edition. Geneva: World Health Organization, World Intellectual Property Organization, World Trade Organization; 2020 (https://medicinespatentpool.org/news-publications-post/launch-of-2nd-edition-of-trilateral-study-on-access-to-medical-technologies-and-innovation-who-wipo-wto/, accessed 18 October 2020).

63. Not even close: issue brief. Geneva: Médecins Sans Frontières; 2017 (https://www.msf.org/sites/msf.org/files/hepc_issuebrief_hep_c_2017.pdf, accessed 17 October 2020).

64. Gilead Pharma corp withdraws investment arbitration after Ukraine agrees to settlement of dispute over monopoly rights to market anti-viral drug. In: Stop Investor–State Dispute Settlement (ISDS) [website] 16 March 2017 (http://isds.bilaterals.org/?gilead-pharma-corp-withdraws&lang=en, accessed 5 February 2018).

65. MedsPaL. Sofosbuvir: Ukraine. In: Medicines Patent Pool [website] (https://www.medspal.org/?keywords=ukraine+velpatas&page=1, accessed 17 October 2020).

66. Patent Opposition Database [website] (https://www.patentoppositions.org/, accessed 17 October 2020).

67. Patent EP2604620 (B1). In: European Patent Office: Espacenet [website] (https://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20160629&DB=EPODOC&locale=en_EP&CC=EP&NR=2604620B1&KC=B1&ND=4#, accessed 17 October 2020).

68. All documents: EP2604620. In: European Patent Office: European Patent Register [website] (https://register.epo.org/application?number=EP13152340&lng=en&tab=main, accessed 17 October 2020).

69. Hepatitis C diagnostic technology landscape. Geneva: WHO; 2019 (https://unitaid.org/assets/HepC-Dx-Tech-Landscape_May2019.pdf, accessed 17 October 2020).

70. Revolutionary approach to diagnostic testing for resource-limited settings. In: Hologic Global Access Initiative [website] (https://www.hologic.com/sites/default/files/SS-00757-001_001_01_Humancare%20GAI%20flashcard.pdf, accessed 17 October 2020).

71. Médecins du Monde (MdM) and Treatment Action Group (TAG). mapCrowd: a new online crowdsourcing platform. In: hepCoalition [website] 29 February 2016 (https://www.hepcoalition.org/advocate/advocacy-tools/article/mapcrowd, accessed 17 October 2020).

72. Gay B. Activist guide to hepatitis C virus diagnostics. New York: Treatment Action Group; October 2019 (https://www.hepcoalition.org/IMG/pdf/tag_activist_guide_to_hcv_diagnostics_final.pdf, accessed 17 October 2020).

73. Who has access to hepatitis C testing? Liberate our diagnostics! Issue brief. mapCrowd; January 2020 (https://en.calameo.com/read/006141377245c4d76cedc?page=1, accessed 17 October 2020).

74. Research references: diagnostics intellectual property and market monopoly landscape. In: MSF Access Campaign [website] (https://msfaccess.org/research-refere nces-diagnostics-intellectual-property-and-market-monopoly-landscape, accessed 17 October 2020).

75. Driehaus J. Patent landscape in molecular diagnostics. In: Storz U, Flasche W, Driehaus J, editors. Intellectual property issues. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012:73–106.

76. Association de lutte contra le SIDA/Londeix P. Diagnosis and monitoring of hepatitis C (HCV) in Morocco: current status and strategies for universal access. 2018 (https://www.alcs.ma/1282-diagnosis-and-monitoring-of-hepatitis-c-hcv-in-morocco, accessed 17 October 2020).

77. Bielen R. Harm reduction and viral hepatitis C in European prisons: a cross-sectional survey of 25 countries. Harm Reduct J. 2018;15:25 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5948815/, accessed 20 May 2020).

78. Assessment of the viral hepatitis response in Ukraine. Mission report, 6–9 June 2017. Copenhagen: WHO Regional Office for Europe; 2018 (http://www.euro.who.int/__data/assets/pdf_file/0007/372697/ukr-hepatitis-report-eng.PDF?ua=1, accessed 26 May 2020).

79. Mahmud S, Akbarzadeh V, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Iran: systematic review and meta-analyses. Sci Rep. 2018;8:150 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5760657/, accessed 26 May 2020).

80. Iversen J, Grebely J, Catlett B, Cunningham P, Dore GJ, Maher L. Estimating the cascade of hepatitis C testing, care and treatment among people who inject drugs in Australia. Int J Drug Policy. 2017;47:77–85 (https://pubmed.ncbi.nlm.nih.gov/28578863/, accessed 26 May 2020).

81. Iversen J, Wandan H, Topp L, Kaldor J,Maher L. Reduction in HCV incidence among injection drug users attending needle and syringe programs in Australia: a linkage study. Am J Public Health. 2013;103(8):1436–44.

82. Coupland H, White B, Bates A, Park JN, Iversen J, Maher L. Engaging people who inject drugs in hepatitis C virus testing and prevention through community-based outreach in Sydney, Australia. Drug Alcohol Rev. 2019;38(2):177–84 (https://pubmed.ncbi.nlm.nih.gov/30652363/?from_term=%28hepatitis+C%29+AND+%28injecting%29&from_sort=&from_page=5&from_pos=6, accessed 26 May 2020).

83. Martin NJ, Boerekamps A, Hill AM, Rijnders BJA. Is hepatitis C virus elimination possible among people living with HIV and what will it take to achieve it? JIAS. 2018;21 (S2) (https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25062, accessed 27 May 2020).

84. World Hepatitis Alliance [website] (https://www.worldhepatitisalliance.org, accessed 26 May 2020).

85. Hepatitis C. In: Médecins Sans Frontières [website] (https://www.msf.org/hepatitis-c, accessed 26 May 2020.

86. Update of the mid-term evaluation of the HIV/HCV drug affordability project. Final report. Geneva: Unitaid; 2018 (https://unitaid.org/assets/Update-of-the-mid-term-evaluation-of-the-hiv-hcv-drug-affordability-project.pdf, accessed 26 May 2020).

87. Doctors of the world opposes another sofosbuvir patent. In: Médecins du Monde [website]. 2017. (https://www.medecinsdumonde.org/en/news/2017/03/27/doctors-world-opposes-another-sofosbuvir-patent, accessed 22 June 2020).

88. Hepatitis C. In: Médecins du Monde [website] (https://www.medecinsdumonde.org/en/tags/hepatitis-c , accessed 26 May 2020).

89. Indolfi G, Easterbrook P, Dusheiko G, El-Sayed MH, Jonas MM, Thorne C et al. Hepatitis C virus infection in children and adolescents. Lancet Gastroenterol Hepatol. 2019;4(6):477–87 (https://pubmed.ncbi.nlm.nih.gov/30982721/, accessed 17 June 2020).

90. Nwaohiri A, Schillie S, Bulterys M, Kourtis AP. Towards elimination of hepatitis C virus infection in children. Lancet Child Adolesc Health. 2018;2(4):235–7 (https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(18)30069-5/fulltext, accessed 26 May 2020).

91. FDA approves first treatment for all genotypes of hepatitis C in pediatric patients. U.S. FDA News Release, 30 April 2019. In: U.S. Food and Drug Administration [website] (https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-all-genotypes-hepatitis-c-pediatric-patients, accessed 4 September 2020).

92. Gaudino A. Pipeline report 2020 – HCV treatment. Treatment Action Group; 2020 (https://www.treatmentactiongroup.org/wp-content/uploads/2020/08/pipeline_HCV_treatment_2020.pdf, accessed 3 Sep 2020).

93. Coppola N, Alessio L, Onorato L, Sagnelli C, Macera M, Sagnelli E et al. Epidemiology and management of hepatitis C virus infections in immigrant populations. Infect Dis Poverty. 2019;8:17 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6419370/, accessed 22 June 2020).

94. Edmunds B, Miller ER, Tsourtos G. The distribution and socioeconomic burden of hepatitis C virus in South Australia: a cross-sectional study 2010–2016. BMC Public Health. 2019;19:527 (https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-6847-5, accessed 22 June 2020).

95. Uhanova J, Tate RB, Tataryn DJ, Minuk GY. The epidemiology of hepatitis C in a Canadian Indigenous population. Can J Gastroenterol. 2013;27(6):336–40 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3684368/, accessed 22 June 2020).

96. Pakistan's investment in hepatitis may see return within years. In: World Health Organization: Hepatitis [website]. 2018 (https://www.who.int/hepatitis/news-events/towards-hepatitis-elimination-pakistan/en/, accessed 21 May 2020).

97. Financing prevention, testing and treatment of hepatitis in the context of universal health coverage: report from a satellite meeting at the replenishment conference of the Global Fund to Fight AIDS, Tuberculosis and Malaria. Geneva: WHO; March 2020 (https://www.who.int/publications-detail/financing-prevention-testing-and-treatment-of-hepatitis-gfatm-satellite-report, accessed 28 May 2020).

98. Tordrup D, Hutin Y, Stenberg K, Lauer JA, Hutton DW, Toy M. Additional resource needs for viral hepatitis elimination through universal health coverage: projections in 67 low-income and middle-income countries, 2016–30. Lancet Glob Health. 2019;7(9):e1180–e1188.

99. Hepatitis C co-infection: stopping the major killers of people living with HIV. In: Unitaid [website] (https://unitaid.org/investment-area/hepatitis-c-co-infection/#en, accessed 28 May 2020).

100. Harm reduction for people who use drugs. Geneva: The Global Fund; March 2020 (https://www.theglobalfund.org/media/1279/core_harmreduction_infonote_en.pdf, accessed 22 June 2020).

101. Report of the WHO global partners' meeting on hepatitis elimination, Pregny-Chambesy, 27–28 February 2019. Geneva: WHO; 2019 (https://www.who.int/publications-detail/report-of-the-who-global-partners-meeting-on-hepatitis-elimination, accessed 28 May 2020).

102. Global AIDS update 2018. Miles to go: closing gaps, breaking barriers, righting injustices. Geneva: UNAIDS; 2018 (https://www.unaids.org/en/resources/documents/2018/global-aids-update; accessed 13 July 2020).

103. Considerations for adoption and use of multidisease testing devices in integrated laboratory networks. Geneva: World Health Organization; 2017 (https://www.who.int/tb/publications/2017/considerations_multidisease_testing_devices_2017/en/ ; accessed 13 July 2020).

104. Daklinza® US FDA label. February 2017 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/206843s006lbl.pdf, accessed 6 February 2018).

105. 4th Invitation to manufacturers and suppliers of medicinal products for treatment of hepatitis B and C, to submit an Expression of Interest (EEOI) for product evaluation to the WHO Prequalification Team: medicines. Geneva: WHO Prequalification Team; 3 April 2017 (https://extranet.who.int/prequal/sites/default/files/documents/142_EOI%20hep%20B%26C_April2017_0.pdf, accessed 17 October 2020).

106. Daclatasvir. In: Medicines Patent Pool [website] (https://medicinespatentpool.org/licence-post/daclatasvir-dac/, accessed 18 June 2020).

107. Mavyret® US FDA label. August 2017 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209394s000lbl.pdf, accessed 17 October 2020).

108. Sovaldi® US FDA label. March 2015 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204671s004lbl.pdf, accessed 6 February 2018).

109. Sovaldi® registration in the developing world. Gilead (https://www.gilead.com/-/media/files/pdfs/aoem-registrations/sovaldi_registeration.pdf?la=en&hash=A1C56DDC36C8388E5D08EC9355A0C320; accessed 15 July 2020).

110. Harvoni® US FDA label. March 2015 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205834s001lbl.pdf, accessed 17 October 2020).

111. Harvoni® registration in the developing world. Gilead (https://www.gilead.com/-/media/files/pdfs/aoem-registrations/harvoni_registeration.pdf?id=2&la=en&hash=9D9E167E17132DDB1A9E9A039D630D50; accessed 15 July 2020).

112. Epclusa® US FDA label. June 2016 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208341s000lbl.pdf, accessed 6 February 2018).

113. Vosevi® US FDA label. July 2017 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209195s000lbl.pdf, accessed 6 February 2018).

114. Vosevi® registration in the developing world. Gilead (https://www.gilead.com/-/media/files/pdfs/aoem-registrations/vosevi_registeration.pdf?la=en&hash=0F45D9226E2AD9880DCA566D27AA0FE3; accessed 13 July 2020).

For more information, contact:

World Health Organization
Department of HIV and Global Hepatitis Programme
20, avenue Appia
1211 Geneva 27
Switzerland

Email: hiv-aids@who.int
who.int/hiv
who.int/hepatitis
who.int/reproductivehealth/topics/rtis

9789240019003