Unitaid
Innovation in Global Health

World Health Organization

TECHNOLOGY AND MARKET LANDSCAPE

HEPATITIS C MEDICINES

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(Acting as the host organization for the Secretariat of Unitaid)

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Contents

Foreword

In October 2013, Unitaid published a scoping paper on hepatitis C. At the time, two direct-acting antiviral medicines were on the market. While these improved therapeutic options at the time, that improvement was limited by the fact that these medicines needed to be used with pegylated interferon and ribavirin – medicines that can cause considerable side-effects.

In February 2015, Unitaid published its first technology and market landscape of HCV medicines. By then, the role of those first direct-acting antivirals had significantly diminished, and nine new direct-acting antivirals had been launched – though they were available only in a limited number of countries. The February 2015 report – and an update published in November 2015 – took stock of this rapidly changing market where new products had the potential to become "blockbusters" almost overnight but also risked becoming quickly outdated due to superior products entering the market.

The market for HCV medicines continues to develop and is changing rapidly as the launch of new treatments continues. Short, interferon- and ribavirin-free, pan-genotypic regimens that can be used for most patients – and that are suitable for use in resource-limited settings – are now on the market. At the same time, some consolidation is taking place, and the relative importance of products and regimens is becoming clearer.

Despite these advances, access challenges remain. In fact, the challenges too have evolved – from a uniform problem of medicines being too expensive, to a more diverse range of challenges that varies between countries. Unitaid believes that these multifaceted challenges can and should be addressed to ensure that HCV medicines will be available to all who need them.

Consequently, it is timely to publish this updated version of the HCV medicines technology and market landscape.

Abbreviations

AASLD	American Association for the Study of Liver Disease
API	Active pharmaceutical ingredient
ART	Antiretroviral therapy
ARVs	Antiretroviral medicines
CL	Compulsory licence
DAA	Direct-acting antiviral
DCV	Daclatasvir
EASL	European Society for the Study of Liver Diseases
ELB	Elbasvir
FDC	Fixed-dose combination
GLE	Glecaprevir
GZR	Grazoprevir
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDSA	Infectious Diseases Society of America
LDV	Ledipasvir
mg	Milligram
OST	Opioid substitution therapy
Peg-IFN	Pegylated interferon
PEPFAR	(United States) President's Emergency Plan for AIDS Relief
PIB	Pibrentasvir
Q	Quarter (-year)
r	Ritonavir
RAS	Resistance-associated substitutions
RBV	Ribavirin
RNA	Ribonucleic acid
ROW	Rest of the world
SIM	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virological response
USA	United States of America
USFDA	United States Food and Drug Administration
VEL	Velpatasvir
VOX	Voxilaprevir
WHO	World Health Organization

Executive Summary

Hepatitis C virus (HCV) is a major global health problem. WHO estimates that 71 million people worldwide are chronically infected with HCV. Of those, 2.3 million people are coinfected with the human immunodeficiency virus (HIV) and HCV. In 2015, around 400 000 people died of HCV-related liver disease, and evidence indicates that the HCV burden is increasing.

Direct acting antivirals (DAAs) have revolutionized treatment for hepatitis C. Combinations of DAAs can cure infection with HCV in 12 weeks, are highly effective and have limited side-effects. Pan-genotypic combinations (that are effective against all genotypes of HCV) have started to become available; they can contribute to the simplification of both the diagnostic and treatment algorithm, which would enable treatment to be rolled out in resource-limited settings.

The market for direct-acting antivirals (DAAs) has significantly changed in the few years since they were launched. The relative importance of regimens is becoming clearer. New DAAs and combinations thereof continue to be launched, expanding the number of regimens. Nevertheless, to date, sofosbuvir still is the backbone of most regimens.

DAAs are becoming available in more low- and middle-income countries, although the pace should be quickened. There is still a long way to go until all key products are registered and launched in all countries.

Affordability of DAAs has improved significantly, but access remains limited. Initially, due to their high prices, affordability of DAAs was limited in high-, middle- and low-income countries alike. Now there is a divide between those countries where, because of intellectual property barriers, prices have remained (very) high and other countries where generics are, or can be, available at much lower prices. The result is a dual market.

Where prices remain high, countries are rationing access or looking for other ways to contain costs, such as negotiating prices, concluding volume/price deals or exploring compulsory licensing. These strategies have varying degrees of success. Where DAAs are provided only to patients who are most in need of treatment – generally, the backlog of previously diagnosed patients[1] and those with advanced liver disease – volumes tend to level off (after an initial peak) while willingness to pay may decline.

Where generics are available at affordable prices, financing is lacking. In countries where intellectual property rights are not a barrier or where licences enable generic competition, DAA prices are starting to approach the lowest sustainable level, and a cure for HCV is no more costly than a year of first-line HIV treatment. However, many of these countries lack financing for the treatment of hepatitis C. This is often compounded by other hurdles, most notably a lack of awareness about hepatitis C among patients and policy-makers, limited health system readiness, high (out-of-pocket) cost of diagnosis, and a lack of screening.

Some patients take matters in their own hands. Rather than waiting to become eligible for treatment to be provided to them, they travel to countries where they can purchase DAAs at prices they can afford. Patients are also ordering DAAs online or buy them through "buyers' clubs" that facilitate access for individual patients. In some cases, institutional actors refer patients to buyers' clubs. While such imports are allowed in most countries, these purchases bypass regulatory and quality control systems, as well as treatment guidelines, in "importing" countries.

[1] Before the launch of DAAs, patients diagnosed with HCV who could afford to wait were often not treated with pegylated-interferon-based regimens, but were made to wait for DAAs to become available, as treatment with DAAs has fewer side-effects and higher cure rates.

Meanwhile, most countries struggle to find the people with HCV infection after they have treated the initial peak of previously diagnosed (backlog) patients. This is because of a lack of screening and a lack of awareness of or demand for HCV testing. It situation is compounded by the fact that large-scale screening programmes are expensive.

Prioritization of high-risk groups that can be reached for HCV screening, diagnosis and treatment **could be a way forward**, and some "pathfinder" countries are reportedly considering this approach. Groups at high risk for HCV infection include, among others, people living with HIV, people who inject drugs, prisoners and children born to HCV-positive mothers. Offering HCV screening in, for instance, ART clinics and harm reduction services may therefore have the dual effect/benefit of facilitating the finding of HCV-positive patients and reducing new infections (as some of these groups are driving the HCV epidemic).

The market for generics has developed fast but remains fragile, because of the various challenges related to demand and uptake that result in uncertain volumes. The large number of generic suppliers of some DAAs, resulting in significant competition, appears to contribute to this uncertainty (while also spurring price decreases). Even so, since mid-2016, more patients were treated with generics than with originator DAAs.

Introduction

Unitaid was created in 2006 to facilitate access to commodities needed to treat human immunodeficiency virus (HIV), tuberculosis (TB) and malaria. In 2013, Unitaid started looking at hepatitis C virus (HCV) in the context of HIV/HCV coinfections. People with living with HIV are around six times more likely to have HCV infection than those who are not HIV-positive, and they progress faster to serious liver disease. As a result, HCV is increasingly becoming a cause of mortality for people living with HIV, and especially those who are receiving HIV treatment. Moreover, there were – and still are – clear market challenges related to HCV commodities that inhibit access.

Unitaid has a mandate to work on HCV in the context of HIV coinfection. Through this mandate, Unitaid seeks to address market problems and, thus, to contribute to the goal of elimination of hepatitis C as a public health problem by 2030.

This landscape analysis provides an overview of the current state of technologies for the treatment of HCV, as well as of the market dynamics that affect access to HCV medicines. It will help identify potential opportunities for investment.

Following a brief description of the methodology, chapters 1–3 of the report provide a short overview of the public health problem of HCV infection, the global goals and the factors that affect uptake of new treatments. Chapter 4 summarizes current knowledge of the fast-evolving landscape of approved and pipeline HCV treatments, comparing each to the target profile for an optimally effective and scalable HCV treatment regimen. Chapter 5 provides an overview of the market dynamics associated with HCV treatments, including supply, demand and factors that affect the affordability, accessibility and uptake of the treatments.

Methodology and acknowledgements

This landscape has been developed on the basis of an extensive desk review of published and grey literature, sup¬plemented by interviews with key informants with knowledge of the state of the art of existing and pipeline technologies. Data and analysis are current as 31 July 2017, unless otherwise indicated.

This landscape was prepared by Andrew Hill, Tracy Swan and Karin Timmermans.

The technology landscape chapter, including the relevant annexes, was prepared by Tracy Swan and Andrew Hill. The chapter is based on information in the public domain – including published and unpublished reports and articles, peer-reviewed publications, regulatory and developer websites, mainstream media articles, and the databases of clinicaltrials.gov and the United States Food and Drug Administration (USFDA). Presentations at major scientific conferences were also incorporated to capture developments that have yet to be published in peer-reviewed literature.

The market landscape chapter, including the relevant annexes, was prepared by Karin Timmermans. The chapter is based on a review of the market literature, websites of medicines regulatory agencies and financial and regulatory filings (e.g. mandatory filings before the United States Securities and Exchange Commission), company websites and press releases, and companies' quarterly financial results.

The estimates of the cost of production of DAAs were prepared by Andrew Hill. Sara Padidar helped with collecting data on the registration status of medicines.

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1. Public health problem

HCV is a serious health problem. With transmission patterns that overlap with those for HIV, HCV is about twice as prevalent as HIV. Although the overall burden and nature of HCV infection varies within and between countries and regions, the HCV problem is worldwide in scope, representing a major cause of morbidity and mortality both for people living with HIV and for HIV-uninfected persons.

Although the transmission and pathogenesis of HCV are well understood, important gaps in data undermine efforts to obtain a clear picture of the HCV epidemic. In 2013, around half (49%) of countries reported having a national surveillance system in place for chronic HCV [*1*]. Among countries that track hepatitis-related cases and deaths, around 50% do not differentiate between the different types of hepatitis (i.e. A, B, C, D, E) [*1*].

Basic facts about hepatitis C virus

HCV is a bloodborne virus that infects liver cells, resulting in illness that ranges from mild and transient to chronic and life-threatening [*2, 3*]. Through bloodborne routes, HCV transmission is 10 times more efficient than HIV transmission [*4*]. HCV establishes infection in liver cells by using proteins on its protective coating to attach to a receptor site on the cell surface. Through enzymes and other means, HCV replicates itself and infects additional liver cells.

Acute HCV infection occurs within 2 weeks to 6 months following initial exposure to the virus. Some 80% of persons with acute HCV infection exhibit no symptoms. An estimated 15 – 45% of persons with acute HCV infection mount an immune response that effectively clears the virus within 6 months of infection [*2*]. However, although no longer infected, persons who cleared HCV infection will still test positive on HCV antibody screening tests.

Infected persons who do not naturally clear the infection develop chronic HCV infection. This lifelong infection can result in cirrhosis (i.e. severe scarring of the liver) or liver cancer [*2, 3*]. The World Health Organization (WHO) has identified the primary modes of HCV transmission [*2*], namely:

- *Health care*: Re-use or poor sterilization of medical and dental equipment, especially needles and syringes, is a major source of HCV transmission.

- *Injecting drugs*: The sharing of injecting equipment during drug use is also an important cause of HCV transmission in many countries, including in a growing number of resource-limited settings. Globally, the prevalence of anti-HCV antibodies is 67% among people who inject drugs [*5*].

- *Blood*: In countries where blood donations are not routinely screened for bloodborne pathogens, blood transfusions or other blood products may lead to HCV transmission.

Less common modes of transmission include:

- *Mother-to-child transmission*: HCV-infected pregnant women may pass HCV to their newborns, although the odds of mother-to-child transmission are much lower for HCV (4–8 per 100 births by infected mothers) than for untreated HIV (17–25 per 100 births). The risk of HCV transmission is higher (10–25 per 100 births) in HIV/HCV coinfected mothers [*5*].HCV is not transmitted through breastmilk [*2*].

- *Tattooing, circumcision*: HCV transmission has also been linked to tattooing, body piercing and circumcision when the equipment or ink used are not sterile [*5*].

- *Acquisition by health-care workers:* for instance, through accidents such as needle-stick injuries [*5, 6*].

- *Sexual activity:* sexual transmission of HCV among HIV-negative people is uncommon; however, HIV-positive people, particularly men who have sex with men, are at increased risk of HCV infection through unprotected sex [*5, 7*].

HCV cannot be transmitted through hugging, kissing or sharing food or drinks with an infected person [*2*].

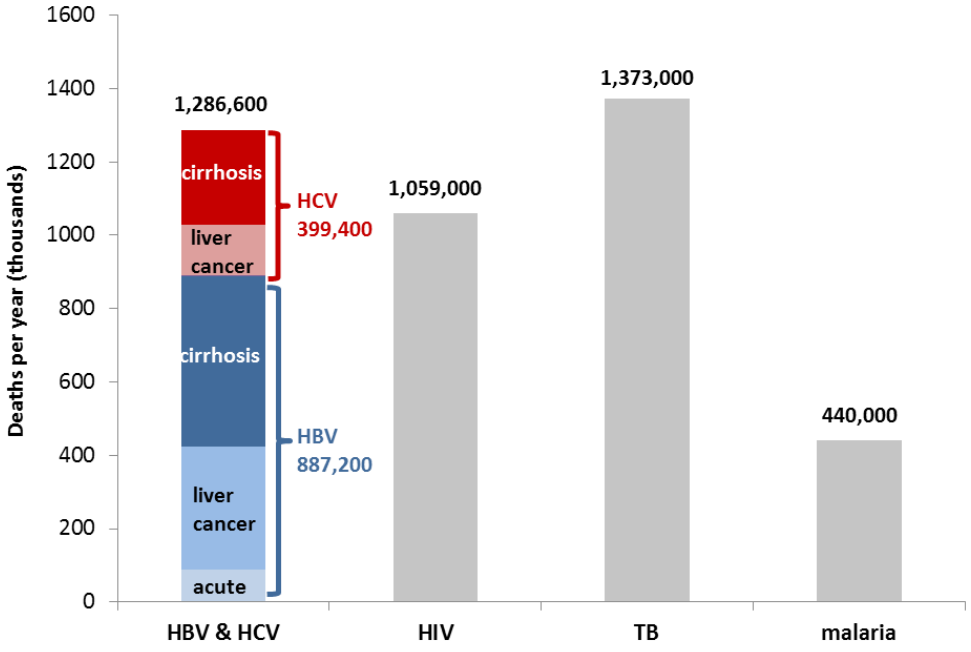
No vaccine is available for the prevention of HCV infection.

Global health burden associated with hepatitis C virus

Estimates of the number of persons with HCV infection vary, reflecting the lack of data on HCV from many countries. Globally, HCV antibody prevalence is estimated to be between 1.6% and 2.8% [*8, 9*].

WHO estimates that, globally, 71 million people have chronic HCV infection, and that 1.75 million new HCV infections occur each year [*10*]. The prevalence of HCV varies considerably between regions. Although data are limited, high viraemic prevalence (above 3%) has been reported in Central Asia and Eastern Europe. Viraemic prevalence is also relatively high in central sub-Saharan Africa (2.1%), North Africa/Middle East (1.7%), and western sub-Saharan Africa (1.3%). In most other parts of the world, HCV prevalence reportedly ranges between 0.5 and 1.0% [*11*]. Global prevalence of HCV is estimated to be 1.0% [*10, 11*].

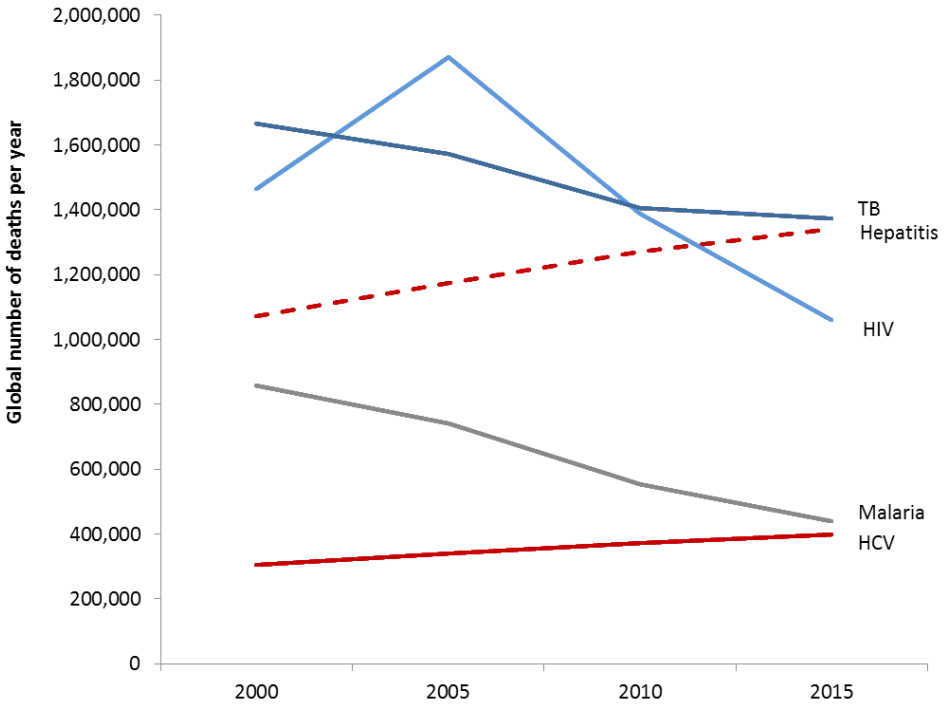
FIGURE 1.
BURDEN OF HEPATITIS B AND C



Source of data: WHO. Global health estimates 2015: estimated deaths by age, sex and cause.

HCV is an important source of morbidity and mortality (see Figure 1). WHO estimates that in 2015 around 400 000 people died of HCV-related liver disease.[2] Since 2000, the number of deaths from HCV has increased, while over the same the total worldwide number of deaths from HIV, TB and malaria fell (see Figure 2) [*10*].

FIGURE 2.
TRENDS IN WORLDWIDE DEATHS FROM HIV, TUBERCULOSIS, MALARIA AND VIRAL HEPATITIS



Source : WHO. Global health estimates 2015: estimated deaths by age, sex and cause.

Some 15–30% of persons with chronic HCV infection will develop cirrhosis within 20 years. Every year, 2–4% of those with cirrhosis will develop liver cancer [*5*]. Between 1990 and 2013, of all cancers, only liver cancer caused by HCV increased substantially (by 125%) [*12*].

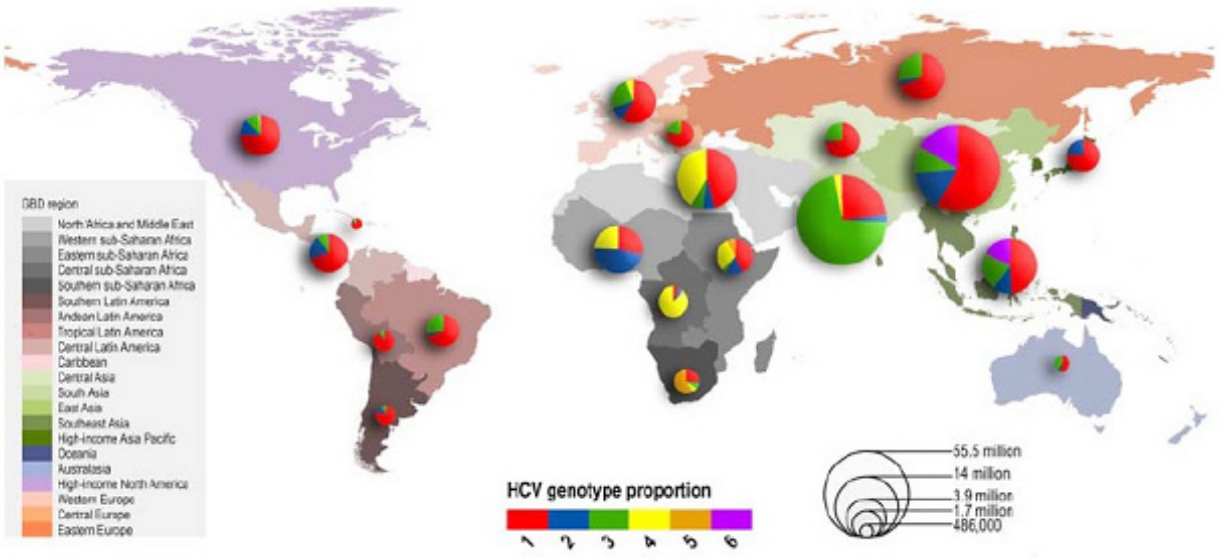
Certain populations are especially heavily affected by HCV. Globally, two in three (67%) people who are injecting drugs are infected with HCV [*5*]. HCV prevalence is also higher in some populations of HIV-positive men who have sex with men [*13*].

[2] Until recently, WHO and others relied on (higher) Global Burden of Disease estimates [*10, 12*].

Patterns of transmission vary across the globe. In low- and middle-income countries, health-related interventions – such as blood transfusions, dialysis and injections of medicines – are important sources of HCV transmission [*5, 14*]. Frequent injections, especially where infection control practices are suboptimal, facilitate rapid HCV transmission. In some regions of Egypt, for example, almost 15% of the population is infected with HCV [*5*]. In high- and middle-income countries, many HCV infections occur among injecting drug users, although recent years have seen a notable increase in transmission among HIV-positive men who have sex with men [*13, 15*].

There are six primary genotypes of the virus (and multiple subtypes). Genotypes 1 and 3 are the most prevalent, accounting for 46.2% and 30.1% of HCV cases worldwide, respectively [*16*]. Together, genotypes 2, 4 and 6 represent 22.8% of HCV cases, while genotype 5 accounts for less than 1% [*16*]. Within regions, substantial variation in genotype distribution is apparent (Figure 3).

FIGURE 3.
GLOBAL DISTRIBUTION OF HCV GENOTYPES 1–6.



Source : Messina JP et al. Global distribution and prevalence of hepatitis C virus. Hepatology. 2015;61(1):77–87.

Human immunodeficiency virus/hepatitis C virus coinfection

The HCV and HIV epidemics interact in several ways. For instance, the two viruses share some transmission routes. HIV-positive men who have sex with men appear to be more likely to contract HCV than their HIV-uninfected peers, and pregnant women living with HIV are similarly more likely than HIV-negative pregnant women to pass the virus along to their newborns if they are not on antiretroviral therapy (ART). Overall, people living with HIV are about six times more likely to have HCV than people who are HIV-negative [*17*].

Worldwide, around 2.3 million people are coinfected with HIV and HCV [*10*]. Among populations of HIV-positive individuals who inject drugs, it is common to find that HCV prevalence exceeds 80% [*18*].

Rates of coinfection tend to be closely related to overlapping risk patterns for HIV and HCV. Countries where people who inject drugs and men who have sex with men are at highest risk for HIV usually have the highest rates of coinfection [*19–21*]. However, these populations are often still heavily affected by HIV/HCV coinfection even where overall coinfection rates are low.

Coinfection has important clinical consequences. HIV infection accelerates the progression of HCV-related cirrhosis and fibrosis [*22–27*]. Whether HCV has an effect on the progression of HIV remains uncertain, with studies reaching conflicting conclusions. However, it is clear that HCV worsens health outcomes for people living with HIV and increases all-cause AIDS-related and liver-related morbidity, hospitalization rates and mortality in this population, even among people receiving ART [*28–35*]. Even when on ART, the risk of hepatic decompensation among HIV/HCV coinfected people is higher than among HCV monoinfected people [*5*].

Ironically, even as ART has dramatically improved HIV-related clinical prospects, its scale-up has increased the incidence of HCV-related complications among people living with HIV because coinfected persons who in earlier years would have died of AIDS are now living long enough to experience severe liver damage as a result of chronic HCV infection. In settings where access to ART is widespread, HCV-related end-stage liver disease is now a leading cause of death among people living with HIV [*31, 32, 34, 36, 37*]. This pattern has been especially pronounced in high-income countries, where HIV treatment

has been widespread for roughly two decades. Although only limited data are available from low- and middle-income countries where HIV treatment has more recently been expanded, increased longevity associated with ART may also lead to increased incidence of HCV-associated end-stage liver disease in those countries.

Other hepatitis C virus coinfections

Though the worldwide prevalence of hepatitis B virus (HBV) and HCV coinfection is unknown due to shared modes of transmission, HBV/HCV coinfection is not uncommon in highly endemic areas [*5, 35*]. Both also are coinfections of HIV (see Table 1).

TABLE 1.
Epidemics of HIV, HBV and HCV (in millions)

	HBV	HCV	HIV
HBV	**257**		
HCV	~2.6[3]	**71**	
HIV	2.7	2.3	**36.7**

Coinfection of TB and HCV has also been reported; one study in Egypt found that 17% of newly diagnosed TB patients also had HCV infection [*38*]. A retrospective (postmortem) study of people with TB (78% of whom were prisoners) found that nearly 35% also had HCV infection [*39*]. It is estimated that two out of three people who inject drugs and who develop TB also have HCV antibodies [*5, 40*].

[3] WHO estimates that 1% of the world population has chronic HCV infection [*10*]. Assuming that this percentage also applies to the 257 million people with chronic HBV, around 2.6 million people would be coinfected with HBV/HCV.

2. Goal and targets

On 25 September 2015, world leaders adopted the Agenda for Sustainable Development, including the Sustainable Development Goals. One of the targets for Goal 3 includes a specific reference to combatting hepatitis.

This was followed, at the World Health Assembly in May 2016, by the adoption of the *Global health sector strategy on viral hepatitis 2016–2021*, which has raised the profile of and increased attention on viral hepatitis. The strategy aims to eliminate viral hepatitis as a major public health threat by 2030 [*18*]. It sets targets that are ambitious but realistic. Some of the key targets for HCV are listed in Table 2.

TABLE 2.

Selected targets from the *Global health sector strategy on viral hepatitis*

	2020 target	**2030 target**
Impact targets		
Incidence: new cases of chronic hepatitis C infections	30% reduction	90% reduction
Mortality: hepatitis C deaths	10% reduction	65% reduction
Service coverage targets		
HCV diagnosis	30%	90%
HCV treatment	3 million people have received HCV treatment	80% of eligible persons with chronic HCV infection are treated

Source : [*18*]. The strategy also contains targets on blood safety, injection safety and harm reduction for people who inject drugs. In addition, there are targets specific to hepatitis B.

3. Factors that can facilitate the uptake of new hepatitis C virus medicines

For a new treatment to become available for use in resource-limited settings, several things need to be in place.

Initial regulatory approval

Initial regulatory approval for a new medicine is usually granted by a regulatory body in a high-income country, such as the United States Food and Drug Administration (USFDA), the European Medicines Agency (EMA) or the Pharmaceuticals and Medical Devices Agency of Japan. In the case of recent advances in HCV treatment, for instance, the USFDA was the first to approve sofosbuvir (SOF), while daclatasvir (DCV) was first approved in Japan. Approval by such regulatory bodies allows a medicine to be marketed only in the country (or countries) over which the regulatory body has jurisdiction (e.g. the USA for the USFDA). However, approval by a stringent regulatory body can prove influential more widely.

WHO guidance

WHO influences the introduction of new medical innovations in low- and middle-income countries through its clinical guidelines, prequalification process and Model List of Essential Medicines. For instance:

- *Guidelines*: In April 2014, WHO produced its first HCV treatment guidelines. The guidelines were updated in 2016 [*5*]. They provide guidance on screening, treatments to be used, clinical monitoring, and considerations for specific populations. In view of the rapidly-evolving HCV treatment landscape and standard of care, another update is expected towards the end of 2017.

- *Model List of Essential Medicines*: WHO's Essential Medicines List contains more than 400 medicines and is revised every two years. The list provides guidance on priority medicines for procurement and use. Interested parties may submit an application to WHO for inclusion of a product in the Essential Medicines List. On the basis of safety and efficacy, and taking into account factors such as disease prevalence, the WHO Expert Committee determines whether to include a new medicine on the list. Pegylated interferon alpha and ribavirin were included on the 18th version of the list which was published in April 2013 [*41*]. The 19th version (April 2015) included many of the direct-acting antivirals (DAAs) that had been launched on the global market at the time (i.e. DCV, dasabuvir, simeprevir, SOF, the fixed-dose combinations ledipasvir/SOF and ombitasvir/paritaprevir/ritonavir) [*42*]. In April 2017, SOF/velpatasvir was added [*43*].

- *Prequalification*: Prequalification by WHO is often a prerequisite for donors to use their funds to purchase a particular medicine. To be eligible for prequalification, medicines or diagnostics must be on the Model List of Essential Medicines or be included in WHO treatment guidelines.[4] WHO evaluates the quality, safety and efficacy of a medical product on the basis of information submitted by the manufacturer. Although primarily intended to assure the quality of medical products procured by United Nations agencies, WHO's list of prequalified medicines has, over time, influenced procurement decisions by donors and national governments. In September 2014, WHO issued for the first time a specific invitation for expressions of interest from manufacturers and suppliers of medicines for HCV (as well as hepatitis B).

- *Patent information*: WHO published reports on the patent status of seven new and pipeline HCV medicines in August 2014 *[44–50]*. These reports provide information on the patents and patent applications pertaining to those medicines for all low- and middle-income countries for which information could be found. The reports were updated in June 2016 *[51–55]*.[5]

Adoption at national level

Registration of a new product in the country where it will be used is a critical step towards making a medicine available for use in clinical settings. As in the case of WHO prequalification, manufacturers must apply for registration of their new products by the relevant regulatory authority. Delays in registration of new products are common in some in low- and middle-income countries, especially where national regulatory authorities are weak [*56*] or under-resourced. Some countries accelerate the registration of WHO-prequalified products.

To guide national procurement decisions and clinical practice, more than 150 countries have their own national lists of essential medicines. Countries also translate international treatment recommendations into national guidelines for clinical practice.

Other crucial prerequisites for a robust HCV response are the existence of a national strategy, and of a system or mechanism for implementing HCV treatment and care. The latter is an important gap in many low- and middle-income countries [*1*], where – because of the multi-step diagnostic pathway, the complexity, cost and low efficacy of the earlier treatments and competing priorities – programmes, systems or facilities for HCV diagnosis and treatment were never created and do not exist (except in tertiary hospitals in major cities). This "legacy of inaction" is a key hurdle that needs to be overcome.

Finally, national patent laws and decisions of the national patent office to grant or reject patents related to HCV medicines also have an impact on access (see Chapter 5).

[4] Currently, the WHO prequalification programme assesses medicines in the following therapeutic areas: diarrhoea, hepatitis, HIV/AIDS, influenza, malaria, neglected tropical diseases, reproductive health and tuberculosis.

[5] In addition, the Medicines Patent Pool has a database on patents and licences that provides regularly updated information on the patent and licensing status of HCV medicines in low- and middle-income countries. This database, called MedsPal, is available at http://www.medspal.org/ .

4. Technology landscape

Overview

Until 2013, the standard of care for treatment of HCV involved a combination of pegylated interferon (Peg-IFN) and ribavirin (RBV). The standard measure of cure for HCV was undetectable HCV ribonucleic acid (RNA) 24 weeks after completing a course of treatment; this is called sustained virological response (SVR).[6] SVR rates for the combination Peg-IFN + RBV were suboptimal, with even lower cure rates reported among HIV/HCV coinfected persons. In addition, the combination is associated with debilitating and often intolerable side-effects that require intensive monitoring. This can be complex and taxing for both patients and clinicians [*57–60*].

There have been profound advances in the medical management of HCV infection in recent years with the development of new oral medicines (i.e. direct-acting antivirals or DAAs). DAAs can cure HCV infection, as measured by SVR. In DAA trials, there was high concordance between SVR-24 and undetectable HCV RNA at 12 weeks after treatment completion (SVR-12); for this reason, the primary endpoint for clinical trials became SVR-12 rather than SVR-24, which expedited HCV drug development. In view of the effectiveness of the DAAs, SVR is now generally measured by undetectable RNA 12 weeks after the end of treatment.[7] SVR reduces AIDS-related, liver-related and non-AIDS-related morbidity and mortality among persons with HIV/HCV coinfection, even when liver disease is advanced [*30, 61, 62*].

The emergence of interferon-free DAA regimens with cure rates exceeding 90%, for both mono-infected and coinfected patients, has changed the standard of care for HCV [*5, 63–68*]. These newer regimens are safer, more tolerable, simpler and shorter than Peg-IFN + RBV, and they require less intensive monitoring.

Pan-genotypic regimens (i.e. regimens that are effective against all HCV genotypes) in particular are able to simplify HCV treatment. The ideal treatment (see below) should yield cure rates of 90% or more for both mono-infected and coinfected patients across all genotypes

[6] Specifically, SVR after 24 weeks is referred to as SVR-24.
[7] In this report, SVR refers to SVR-12 (12 weeks after the end of treatment), unless otherwise indicated.

as well as in people with cirrhosis. Co-administration with WHO-recommended antiretroviral medicines (ARVs) should be possible and it should be suitable for delivery in existing HIV treatment programmes in resource-limited settings.

Regimens that are (close to) meeting the "ideal" or target profile are already available, and additional regimens are in the pipeline. However, although progress on HCV therapeutics has been transformative, access to DAAs is very limited in most low- and middle-income countries. In addition to delays associated with the multiple steps required for new medicines to become available in developing countries, the high prices of DAAs made them unaffordable for many countries until recently. However, in countries where generic medicines can be used, prices are falling rapidly (see Chapter 5).

Pegylated interferon and ribavirin

Although Peg-IFN + RBV served as the cornerstone of HCV treatment for more than a decade, the combination is far from ideal. Treatment efficacy is suboptimal – with only slightly more than half of the people who start therapy achieving SVR – and varies according to the genotype [*59, 60, 69*]. Efficacy of Peg-IFN + RBV declines as patients have more liver damage (and thus have a more urgent need for treatment), and is notably lower for patients coinfected with HIV.

Treatment with Peg-IFN + RBV is complex and involves weekly injections. It requires extensive monitoring of safety and efficacy, and makes genotyping and assessment of the severity of liver disease necessary. As a result, a number of diagnostic tests must be available. In addition, treatment with Peg-IFN + RBV is commonly associated with side-effects, including serious side-effects that may result in people having to discontinue the treatment.

HCV treatment guidelines in high-income countries now recommend interferon-free therapy [*67, 68*]. WHO's 2016 hepatitis C treatment guidelines do recommend Peg-IFN + RBV + SOF as an alternative regimen for genotype 3 with cirrhosis, and for genotypes 5 and 6 [*5*]. Peg-IFN is likely to be dropped in the forthcoming update of the WHO guidelines.

Direct-acting antivirals

The emergence of a number of DAAs in recent years has allowed the development of highly effective, IFN-free (and at times RBV-free) HCV regimens, dramatically altering the standard of care for HCV treatment. In addition to enhanced tolerability, shorter treatment duration and less intensive monitoring requirements, these regimens generate cure rates substantially greater than those achieved with IFN-based regimens.

Importantly, DAA cure rates are generally the same for HIV/HCV coinfected people as for HCV mono-infected people.

Classes of direct-acting antivirals

Four classes of DAAs target various stages in the HCV lifecycle (see Table 3). Recommended regimens usually combine two or three DAAs from different classes.

TABLE 3.

Classes of DAAs

Class	Mechanism of action	Examples of DAAs
NS3/4A protease inhibitors	Prevent the release of proteins that are essential to viral replication	glecaprevir grazoprevir paritaprevir simeprevir voxilaprevir
nucleoside/tide NS5B polymerase inhibitors	Stop HCV replication by inserting themselves into the virus as it is being assembled	sofosbuvir
non-nucleoside NS5B polymerase inhibitors	Change the shape and inhibit the function of the HCV polymerase enzyme	dasabuvir
NS5A inhibitors	Impede HCV replication through multiple mechanisms, blocking both viral synthesis inside infected cells as well as the assembly and release of HCV virions	daclatasvir elbasvir ledipasvir ombitasvir pibrentasvir velpatasvir

a. Hepatitis C virus protease inhibitors

First-generation HCV protease inhibitors are not pan-genotypic; they are usually effective against HCV genotypes 1 and 4 (although they are less effective against genotype 1a due to a lower resistance barrier). Some of the second-generation protease inhibitors (glecaprevir and voxilaprevir) are pan-genotypic. HCV protease inhibitors are likely to cause gastrointestinal side-effects.

HCV protease inhibitors have a propensity to interact with other drugs. They cannot be co-administered with many commonly-used medications, including some antiretroviral drugs (although they can be used with HIV integrase inhibitors and nucleoside/tide analogs). Despite these limitations, protease inhibitors play an important role in several DAA regimens.

b. Nucleoside/tide polymerase inhibitors

SOF is currently is the only approved nucleotide polymerase inhibitor. It is the backbone of most of the recommended regimens. Additional nucleoside/tide polymerase inhibitors (AL-335 and MK-3683) are currently in phase II trials.

c. NS5A inhibitors

NS5A inhibitors are potent, although they do not have a high genetic barrier to resistance. Baseline resistance to NS5A inhibitors has been seen (at least in genotypes 1, 2, 3 and 4, where they have been most heavily studied), although many people with pre-existing resistance have been cured [*70–73*]. For this reason, NS5A inhibitors are combined with other DAAs that have higher resistance barriers; such regimens have cure rates approaching 100%.

Patients who are unsuccessfully treated with combination regimens that include an NS5A inhibitor frequently have resistance-associated substitutions (RAS) which persist for several years; the longer-term consequences of these remain unclear [*74*].

NS5A inhibitors are taken once daily. They may interact with some antiretroviral medicines, but in some cases can be co-administered. For instance, the dose of daclatasvir needs to be adjusted when taken with efavirenz or ritonavir-boosted atazanavir.

NS5A inhibitors are critical components of safe, pan-genotypic, highly effective and tolerable regimens, in part because some NS5A inhibitors do not require RBV.

d. Non-nucleoside polymerase inhibitors

Only one non-nucleoside polymerase inhibitor, dasabuvir, has reached the market. Earlier candidates were taken twice daily, were active only against genotype 1 with varying potency, and they had a low-to-moderate genetic barrier to resistance.

Recommended treatments

Hepatitis C treatment is changing quickly and treatment guidelines need to be updated frequently. The American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) publish their treatment recommendations online and update them whenever new medicines are approved, new data emerge or indications change.

Hepatitis C treatment guidelines from the European Association for the Study of the Liver (EASL) and WHO are also regularly updated; the latter are currently being revised. Table 4 provides and overview of treatments that are currently recommended. It should be noted that WHO's recommendations were prepared before approval of the fixed-dose combinations of grazoprevir/elbasvir and sofosbuvir/velpatasvir (SOF/VEL).

TABLE 4.

Summary of treatment recommendations from AASLD/IDSA, EASL and WHO [5, 67, 68]

Currently recommended DAA regimensa[a]	HCV genotype					
	G1	G2	G3	G4	G5	G6
elbasvir/grazoprevir*	AASLD EASL			AASLD EASL		
paritaprevir/ombitasvir/r				AASLD EASL WHO		
paritaprevir/ombitasvir/r + dasabuvir	AASLD EASL WHO					
SOF + DCV	AASLD EASL WHO	AASLD EASL WHO	AASLD EASL WHO	EASL WHO	EASL	EASL
SOF/LDV	AASLD EASL WHO			AASLD EASL WHO	AASLD EASL WHO	AASLD EASL WHO
SOF + Peg-IFN					WHO	WHO
SOF + RBV		WHO	WHO			
SOF + SIM	AASLD WHO			EASL WHO		
SOF/VEL*	AASLD EASL	AASLD EASL	AASLD EASL	AASLD EASL	AASLD EASL	AASLD EASL
SOF/VEL/VOX* [+]	AASLD	AASLD	AASLD	AASLD	AASLD	AASLD

Notes : [a] RBV may be recommended with these regimens for certain patient populations.
* Not on the market when WHO guidelines were written.
[+] Included in EASL treatment guidelines as of July 2017, pending marketing authorization by the European Commission.
AASLD = AASLD/ISDA. A blank cell = regimen not recommended for that genotype by AASLD/ISDA, EASL or WHO.

Target product profile

As noted above, combinations of two or more DAAs are to be used in order to ensure efficacy and reduce the risk that resistance could develop. To assess HCV therapies (existing ones as well as those in the pipeline), it is helpful to identify the ideal, or target, profile for HCV regimens for use in resource-limited settings. The ideal HCV treatment would fulfil the following requirements:

- *Safe and tolerable* – definitely IFN-free and preferably RBV-free (to avoid side-effects associated with RBV), and safe for use in pregnant women,[8] children, HIV/HCV coinfected persons and patients with cirrhosis.

- *Pan-genotypic*–effective across all six major HCV genotypes, eliminating the need to test for the HCV genotype.

- *Effective and durable* – with high potency and a high genetic barrier to resistance (i.e. it is unlikely that HCV would develop resistance to the medicine(s) with proper treatment adherence), and associated with SVR rates of at least 90% in all genotypes[9] (see Figure 4).

- *Simple* – having a short duration (no more than 12 weeks), minimal requirements for pre-treatment assessment or safety/efficacy monitoring during and after treatment, ideally a once-daily fixed-dose combination (FDC), and manageable drug – drug interactions with ARVs, opioid substitution therapy (OST) and other commonly-used medications.

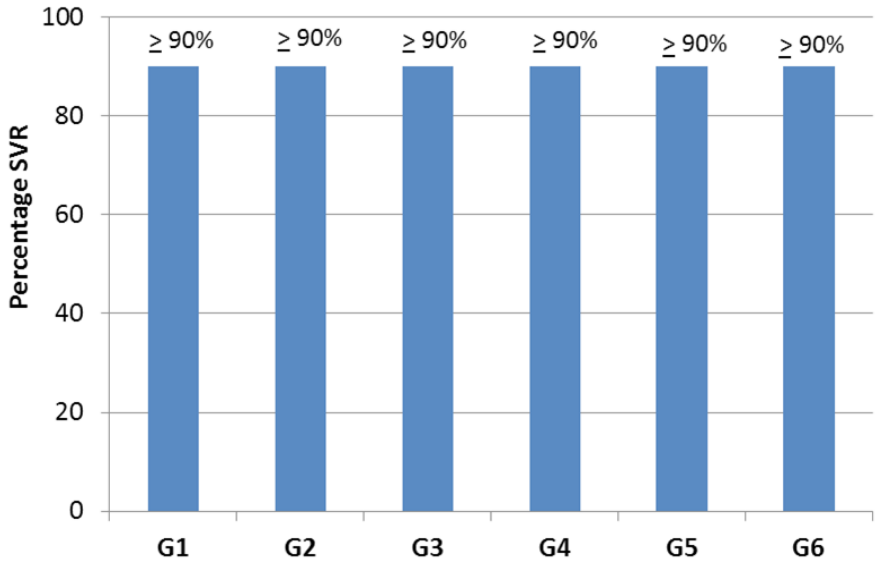
- *Affordable*–to the people who need HCV treatment, their communities and countries.

- *Stable–at both high and low temperatures*

[8] RBV should not be used in women who are, or are planning to become, pregnant or in men who wish to have children. Data are needed on the safety of RBV-free DAA treatment during pregnancy and breastfeeding.
[9] In patients who are the most difficult to treat (i.e. those with decompensated cirrhosis), efficacy should be at least 80%.

FIGURE 4.

TARGET PRODUCT PROFILE: SVR OF THE IDEAL TREATMENT REGIMEN



Pan-genotypic regimens will simplify procurement and delivery of HCV treatment, especially when the duration of treatment does not vary by genotype or stage of liver disease. Safe and efficacious pan-genotypic regimens will also simplify the complex diagnostic algorithm by avoiding the need for pre-treatment genotyping.

In addition, it is important that HCV medicines are of assured quality and meet the quality standards set by WHO (or comparable standards).

Combination regimens versus target product profiles

As in the case of ART for HIV infection, HCV infection needs to be treated with a combination of DAAs of different classes. This section describes combinations currently recommended and in use, as well as some regimens that are about to be launched, and assesses them against the target profile discussed above.

Currently, six SOF-based regimens and three non-SOF-based regimens have been approved. SOF-based regimens dominate as they generally achieve high cure rates, although lower SVR rates have been found in patients with cirrhosis and genotype 3. For all SOF-based combinations, there are limited data regarding treatment outcomes in genotypes 5 and 6.

For a short description of single-ingredient DAAs that are on the market, see Annex 1. Additional information on key products/regimens can be found in Annex 2.

a. Pan-genotypic and potentially pan-genotypic regimens

Sofosbuvir + daclatasvir

The combination SOF + DCV is a potentially pan-genotypic, once-daily regimen. In clinical trials, this combination was safe and tolerable, simple to administer and take, and effective. Numerous reports of the use of SOF + DCV in clinical practice confirm its safety, effectiveness and tolerability. Questions remain about optimal duration of treatment and the addition of RBV in people with cirrhosis. Currently, three strategies are being used, namely:

- 12 weeks of SOF + DCV + RBV ;
- 24 weeks of SOF + DCV ;
- 24 weeks of SOF + DCV + RBV ;

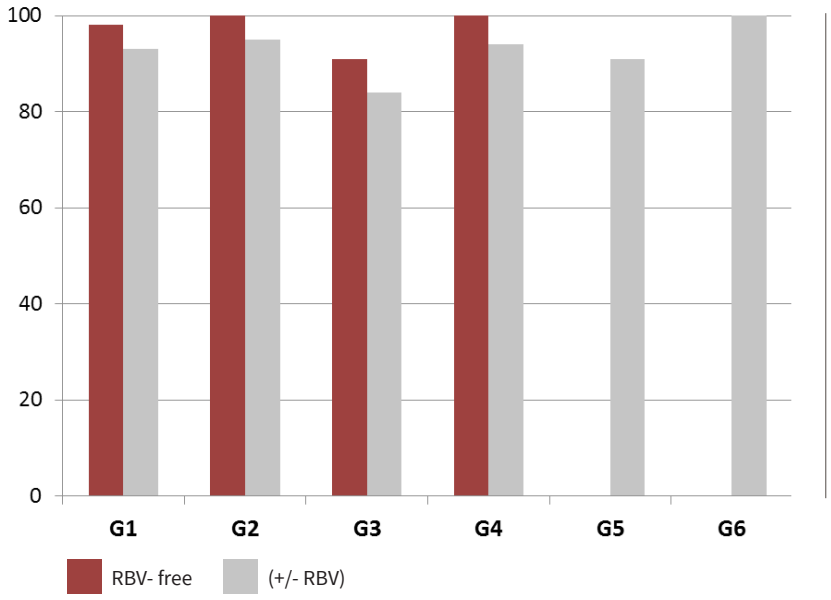
More data (see Annex 3) are now available on persons with genotypes 4, 5 and 6, and persons with pre-cirrhosis (Metavir score F3), compensated or decompensated cirrhosis, who are likely to be prioritized in places where treatment access is limited.

The combination of SOF + DCV can be used with some WHO-recommended ARVs. Dose-adjustment is needed with certain ARVs (efavirenz, nevirapine and atazanavir/ritonavir). For an assessment of SOF + DCV versus the target product profile, see Annex 4.

Some generic companies are developing, or are already marketing, fixed-dose combinations of SOF/DCV (see Annex 13).

FIGURE 5.

SOFOSBUVIR + DACLATASVIR: SVR AFTER 12 OR 24 WEEKS OF TREATMENT



SVR rates (No of patients)	RBV-free	+/- RBV
G1	98% (219)	93% (1575)
G2	100% (13)	95% (22)
G3	91% (151)	84% (752)
G4	100% (3)	94% (316)
G5	––	91% (70)
G6	––	100% (5)

Source of data: *[75, 76].*
Notes: G = genotype . No bar indicates no data (not "zero efficacy").

Sofosbuvir / velpatasvir

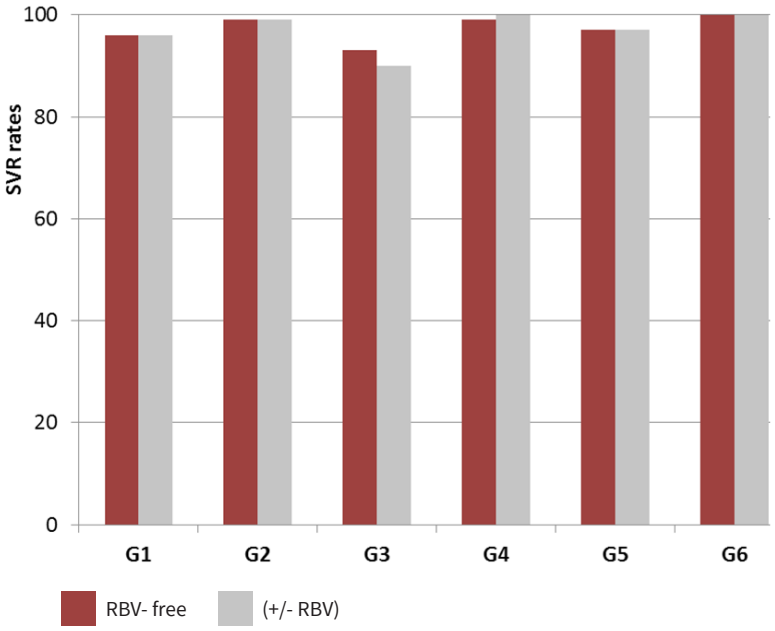
Epclusa®, a pan-genotypic FDC combining SOF with the NS5A inhibitor velpatasvir (VEL) was approved by the USFDA in June 2016 and by the EMA in July 2016.

Treatment duration with SOF/VEL is 12 weeks, regardless of genotype, liver disease stage or HCV treatment history. RBV needs to be added for persons with decompensated cirrhosis. High SVR rates were obtained in clinical trials (see Figure 6) but data on treatment outcomes in clinical practice are not yet available.

The combination SOF/VEL cannot be used with efavirenz. For an assessment of SOF/VEL versus the target product profile, see Annex 4.

FIGURE 6.

SOF/VEL: SVR AFTER 12 WEEKS OF TREATMENT



SVR rates (number of patients)	RBV-free	+/- RBV
G1	96% (896)	96% (778)
G2	99% (343)	99% (261)
G3	93% (645)	90% (592)
G4	99% (183)	100% (128)
G5	97% (35)	97% (35)
G6	100% (51)	100% (42)

Source of data: [76].
Notes: G = genotype

Sofosbuvir / velpatasvir / voxilaprevir

In December 2016, Gilead submitted a new drug application to the USFDA for the fixed-dose combination SOF/VEL/voxilaprevir for treatment of HCV genotypes 1–6 when previous DAA treatment failed. The application also pertains to 8 weeks of treatment for treatment-naïve patients [77].

In January 2017, the EMA reportedly granted accelerated assessment for SOF/VEL/voxilaprevir.

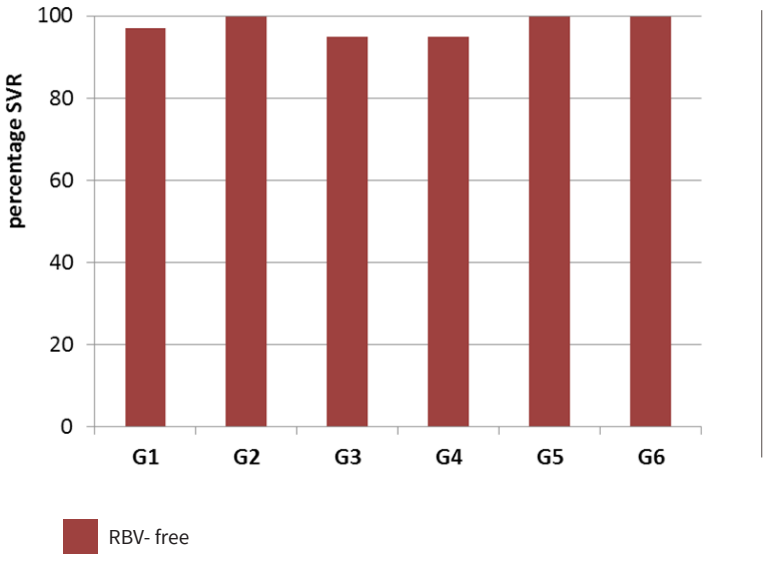
The addition of voxilaprevir (VOX, an HCV protease inhibitor) to the combination SOF/VEL was presumably intended to shorten the duration of treatment. The POLARIS-2 and POLARIS-3 trials compared 8 weeks of treatment with SOF/VEL/VOX versus 12 weeks of treatment with SOF/VEL. POLARIS-2, a 941-person trial in DAA-naïve persons with HCV genotypes 1,2,3,4,5 and 6, included people with compensated cirrhosis (except G3, studied in POLARIS-3). The overall cure rate was higher for 12 weeks of SOF/VEL (98%, or 432/440), versus 8 weeks of SOF/VEL/VOX (95%, or 476/501). The triple regimen was not non-inferior to SOF/VEL.

Of note, there were 21 relapses in people treated with the triplet (mainly in G1a) versus 4 in the SOF/VEL treatment group [*78*]. In POLARIS-3, a trial in 219 treatment-naïve or interferon-experienced persons with HCV genotype 3 and cirrhosis, cure rates were identical (96%) after 8 weeks of SOF/VEL/VOX or 12 weeks of SOF/VEL [*79*].

In July 2017, the USFDA approved the use of Vosevi ® (SOF/VEL/VOX) as 12-week salvage therapy for patients who failed earlier treatment with DAAs [*80*].

FIGURE 7.

SOF/VEL/VOX: SVR AFTER 12 WEEKS TREATMENT



SVR rates (number of patients)	RBV-free
G1	96% (896)
G2	99% (343)
G3	93% (645)
G4	99% (183)
G5	97% (35)
G6	100% (51)

Source of data: [*76*].

Glecaprevir / pibrentasvir

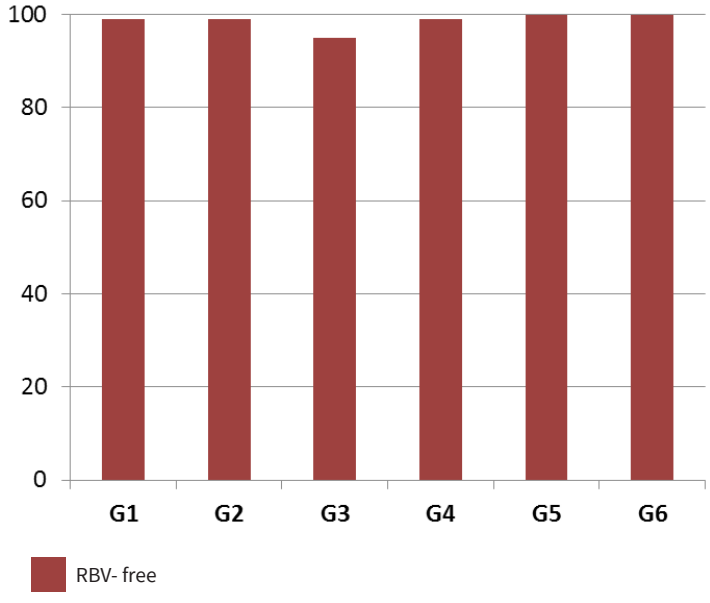
AbbVie's glecaprevir/pibrentasvir (protease inhibitor/NS5A inhibitor) FDC is a once-daily, pan-genotypic regimen. EMA granted marketing approval for the combination (Maviret®) on 28 July 2017, for 8 week treatment of all genotypes of HCV *[81]*.

The regimen has been studied in all HCV genotypes, for 8 or 12 weeks, in people who are treatment-naïve or treatment-experienced. The combination has also been studied in persons with HIV/HCV coinfection, with severe renal impairment, or with compensated cirrhosis. It has also been studied with sofosbuvir, and versus sofosbuvir/daclatasvir in genotype 3. In phase III, cure rates topped 98%, adverse events were generally mild (headache, fatigue, nausea and itching) and treatment discontinuation rates were under 3% (except in severe renal impairment) [*82–85*].

There still are data gaps regarding this regimen: for instance, most phase III studies were carried out in people without cirrhosis, and glecaprevir/pibrentasvir is not recommended for people with decompensated cirrhosis (Child-Pugh Class B or Class C) [*86*]. Data from people with genotype 3 and compensated cirrhosis is limited to phase II results from 135 participants. Drug-drug interactions may limit HIV treatment options. Although both DAAs are active against some NS3 and NS5A resistance, there has been only one phase II trial in people who are NS5A/NS3 treatment-experienced.

FIGURE 8.

GLECAPREVIR/PIBRENTASVIR: SVR AFTER 12–16 WEEKS OF TREATMENT



SVR rates (number of patients)	RBV-free
G1	99% (332)
G2	99% (196)
G3	95% (131)
G4	99% (76)
G5	100% (26)
G6	100% (19)

Source of data: [*76*].

b. Non-pan-genotypic and more complex regimens

Grazoprevir / elbasvir

In January 2016, the US FDA approved Zepatier®, a fixed-dose combination (FDC) of grazoprevir (GZR, a protease inhibitor) and elbasvir (ELB, an NS5A inhibitor), for genotypes 1 and 4. The EMA followed suit in May 2016.

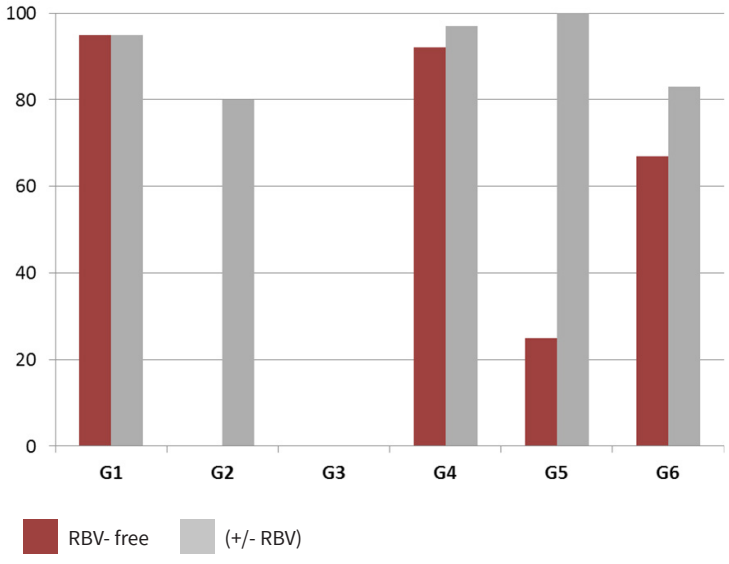
The regimen is complex: in genotype 1, sub-genotyping is recommended, with baseline resistance-testing for persons with HCV genotype 1a (who may need to add RBV, and 4 additional weeks of treatment). RBV is also needed in persons with genotype 1 who are HCV protease-inhibitor-experienced. For treatment-experienced persons with genotype 4, 16 weeks of treatment and the addition of RBV are recommended. This regimen cannot be used in persons with moderate-to-severe hepatic impairment (Child Pugh Class B or Class C) [*87*].

The regimen was safe and highly effective in a placebo-controlled, delayed treatment arm trial of people with renal insufficiency; 99% (115/116) of persons in the immediate treatment arm were cured [*88*]. It has been studied with sofosbuvir in genotype 3, in HIV/HCV coinfection, and in persons who were on opioid substitution and using drugs.

Interactions between GZR/ELB and ARVs limit HIV treatment options during HCV treatment [*65*].

FIGURE 9.

GRAZOPREVIR/ELBASVIR: SVR AFTER 12–18 WEEKS OF TREATMENT



SVR rates (number of patients)	RBV-free	+/- RBV
G1	95% (1789)	95% (506)
G2	––	80% (30)
G3	––	––
G4	92% (96)	97% (33)
G5	25% (4)	100% (4)
G6	67% (64)	83% (6)

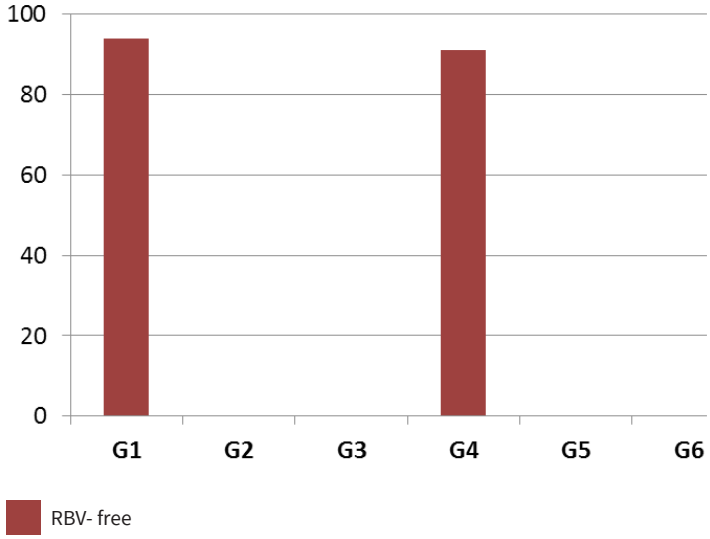
Source of data: [*76*].
Notes: G = genotype. No bar indicates no data (not "zero efficacy").

Ombitasvir / paritaprevir / ritonavir + dasabuvir

In late 2014, the combination of the FDC ombitasvir/paritaprevir/ritonavir (European Union brand name Viekirax®) with dasabuvir (European Union brand name Exviera®) was approved for the treatment of HCV genotype 1, with or without RBV. The copackaged products are marketed in Canada under the brand name Holkira Pak® and in the USA under the brand name Viekira Pak®).

Although high SVR rates have been reported in genotypes 1 and 4 (Figure 10), this regimen is fairly complex; it comprises three tablets in the morning and another in the evening.[10] Persons with HCV genotype 1 need to undergo sub-genotype testing because treatment recommendations vary between genotype 1a and genotype 1b. Persons with genotype 1a are required to add twice-daily RBV, and 24 weeks of treatment are required for some patients (i.e. cirrhotic, treatment-experienced with genotype 1a). In addition, there are many drug–drug interactions, including with some WHO-recommended HIV treatments. This regimen is not recommended for persons with Child-Pugh Class B cirrhosis, and is contraindicated in persons with Child-Pugh Class C cirrhosis.

FIGURE 10.
OMBITASVIR/PARITAPREVIR/r + DASABUVIR: SVR AFTER 12 WEEKS OF TREATMENT



SVR rates (number of patients)	RBV-free
G1	94% (493)
G2	––
G3	––
G4	91% (44)
G5	––
G6	––

Sources of data: G1: AVIATOR, PEARL-III, PEARL-IV; G4: PEARL-I (no ABT-333 – dual combination).
Note: G = genotype. No bar indicates no data (not "zero efficacy").

[10] A once-daily XR version has been approved and launched in the USA

Sofosbuvir / ledipasvir

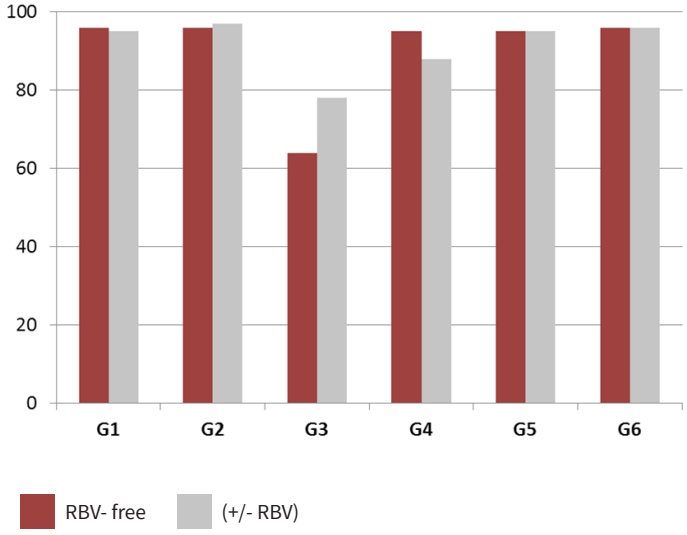
The FDC of sofosbuvir/ledipasvir (SOF/LDV, brand name Harvoni®) makes for a safe, effective, one-pill, once-daily treatment for genotypes 1, 4, 5 and 6. In high-income countries, SOF/LDV cure rates in clinical practice are similar to those obtained during clinical trials. In HCV genotype 1, cure rates among 13 858 people treated with SOF/LDV ± RBV (usually for 12 weeks) ranged from 91% to 98%, although cure rates were lower among people with cirrhosis (92%) [*89*].

In certain patient populations, treatment with SOF/LDV is often shortened to 8 weeks, based on results from the ION-3 trial. In ION-3, 97% of HIV-negative, non-cirrhotic, treatment-naïve persons with HCV RNA ≤ 6 million IU/mL were cured by 8 weeks of treatment [*90, 91*]. In clinical practice, outcomes have varied: cure rates among over 3000 HIV-negative, non-cirrhotic people with HCV RNA < 6 million IU/mL were similar after 8 versus 12 weeks of SOF/LDV [*89, 92*]. However, a 4365-person Veteran's Administration cohort reported significantly lower cure rates with shorter treatment, especially among African-Americans [*93*].

The combination SOF/LDV can be used with some WHO-recommended ARVs, although toxicity monitoring may be required.

FIGURE 11.

SOFOSBUVIR/LEDIPASVIR: SVR AFTER 12–24 WEEKS OF TREATMENT



SVR rates (number of patients)	RBV-free	+/- RBV
G1	96% (1597)	95% (8133)
G2	96% (26)	97% (34)
G3	64% (25)	78% (361)
G4	95% (73)	88% (69)
G5	95% (41)	95% (41)
G6	96% (25)	96% (25)

Sources of data: : *[75, 76].*
Note: G = genotype.

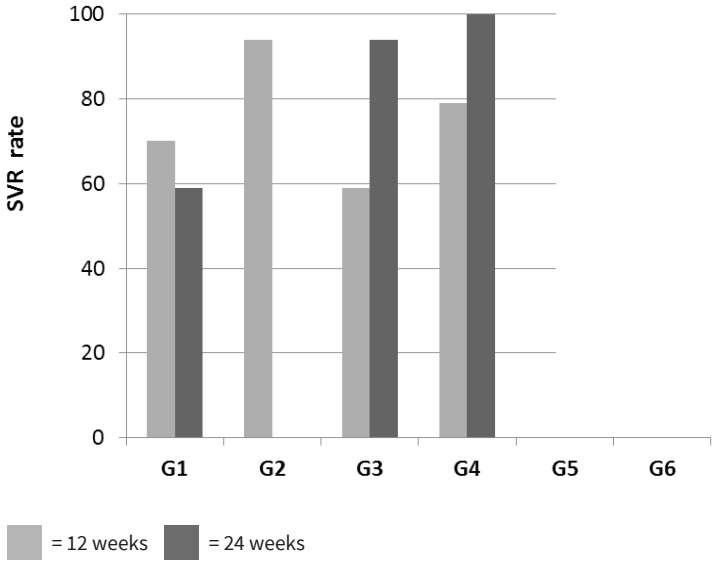
Sofosbuvir + ribavirin

The combination of SOF + RBV is relatively complex and has been replaced by more effective DAA combination regimens. RBV dosing is weight-based; it must be taken twice daily and, while pan-genotypic and comparatively inexpensive, RBV is associated with numerous adverse events – including teratogenicity, renal impairment (requiring dose adjustment), haemolytic anaemia and cardiac events [*94*]. RBV can cause birth defects and fetal death and is contraindicated during pregnancy. Women and their male partners should avoid pregnancy for 6 months after stopping RBV.

Cure rates for SOF + RBV are generally lower than those reported for combinations of DAAs, especially at 12 weeks (Figure 12). The combination also has suboptimal efficacy for patients with genotype 1. With the advent of pan-genotypic, RBV-free regimens, this combination is now considered suboptimal and it is no longer recommended by the AASLD/IDSA and EASL.

FIGURE 12.

SOFOSBUVIR + RBV: SVR AFTER 12 AND 24 WEEKS OF TREATMENT



SVR rates (number of patients)	12 weeks treatment	24 weeks treatment
G1	70% (44)	59% (79)
G2	94% (218)	––
G3	59% (287)	94% (105)
G4	79% (14)	100% (14)
G5	––	––
G6	––	––

Sources of data: G1: SPARE, QUANTUM, VALENCE; G2: POSITRON, VALENCE, FISSION; G3: VALENCE; G4: Ruane et al. [*95*].
Note: G = genotype. No bar indicates no data (not "zero efficacy").

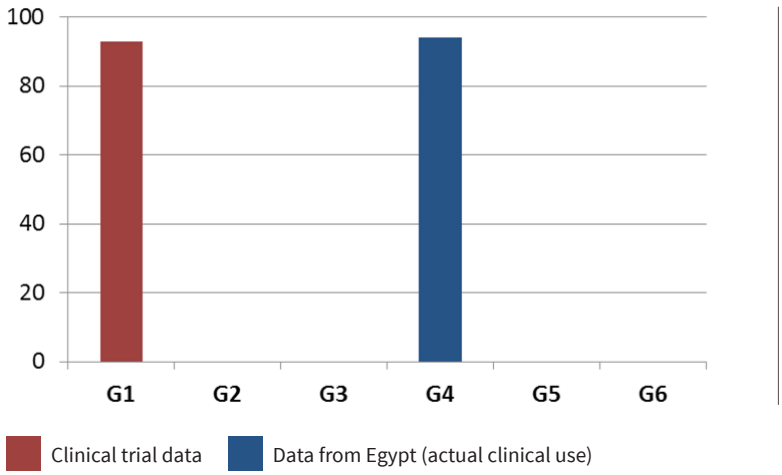
Sofosbuvir + simeprevir

The combination of SOF + SIM (without IFN or RBV) has been approved for the treatment of genotype 1 (USFDA) and for treatment of genotype 1 and 4 (EMA). The standard treatment lasts 12 weeks but is extended to 24 weeks for patients with cirrhosis. This combination has not been studied in HIV/HCV coinfected patients.

Results from 6211 persons with genotype 4, who were treated with 12 weeks of SOF + SIM in government treatment centres in Egypt, were similar to those reported in clinical trials conducted in high-income countries – i.e. 94% were cured [*96*].

FIGURE 13.

SOFOSBUVIR + SIMEPREVIR: SVR AFTER 12 WEEKS OF TREATMENT



SVR rates (number of patients)

G1: 93% (14)

G4: 94% (6211)

Sources of data: G1: COSMOS Cohort 2 – includes null-responders, all patients F3/F4; G4: [*96*].
Note: G = genotype. No bar indicates no data (not "zero efficacy").

c. The role of ribavirin

A number of DAA regimens are used with RBV in certain patients (depending on genotype, sub-genotype, treatment experience, stage of liver disease and other factors). RBV has significant limitations (toxicity, tolerability and teratogenicity), and adding RBV does not always increase cure rates. An analysis of treatment outcomes from RBV-free DAA treatment trials reported cure rates of over 90% without RBV (see Table 5).

TABLE 5.

Cure rates of different DAA regimens in trials, without RBV

Regimen	No. of participants	Cure rate (overall)	Cure rate(G3 only)
SOF + DCV	386 (4 trials)	94.6%	89.4%
SOF/LDV	1787 (15 trials)	94.8%	64%
SOF/VEL	2153 (9 trials)	96.1%	92.7%
glecaprevir/pibrentasvir	935 (6 trials)	98.4%	95.7%*
grazoprevir/elbasvir	1953 (10 trials)	93.8%	--**

Source : *[75,76].* *All were cirrhotic. ** In G3, available data relate to the use of this combination with SOF.

RBV may, however, remain necessary for people with certain sub-genotypes or resistance mutations, in retreatment regimens, or to boost the efficacy of treatment in persons with decompensated cirrhosis, especially in genotype 3. In ASTRAL-4, a trial of SOF/VEL with or without RBV in people with decompensated (Child-Pugh Class B and C) cirrhosis, overall cure rates were higher in persons treated with 12 weeks of SOF/VEL + RBV (94%, or 82/87) than in persons treated for 12 weeks without RBV (83%, or 75/90), or persons treated with 24 weeks of SOF/VEL (86%, or 77/90). The difference in cure rates was greatest in genotype 3, although the number of people was small: 11/13 (85% cure rate) for SOF/VEL/RBV versus 7/14 (50%) and 6/12 (50%) in the other two treatment groups [*97*].

Risks and interactions

Although DAAs are generally very safe, there are special considerations for HIV/HCV coinfected people on ART, for HBV/HCV coinfected persons and during pregnancy.

Interactions between DAAs and ARVs

Although DAAs are safe and effective for people who are HIV/HCV coinfected, drug–drug interactions between ART and hepatitis C treatment must be evaluated to avoid adverse events and HIV or HCV treatment failure [*98*]. An overview of such interactions is presented in Table 6.

TABLE 6.

Interactions between DAAS and WHO-recommended antiretrovirals [88, 95, 99–108].

DAAs	ARVs								
	efavirenz (EFV)*	nevirapine (NVP)	dolutegravir (DTG)	tenofovir (TDF)*	lopinavir/r (LPV/r)	atazanavir/r (ATV/r)	lamivudine/ emtricitabine (3TC/FTC)*	zidovudine (AZT)	abacavir (ABC)
simeprevir	contra-indicated	contra-indicated			contra-indicated	contra-indicated			
sofosbuvir									
daclatasvir	adjust/ monitor	adjust/ monitor				adjust/ monitor			
sofosbuvir/ velpatasvir	contra-indicated	contra-indicated		adjust/ monitor					
sofosbuvir/ velpatasvir voxilaprevir	not recommended	no data available		adjust/ monitor	not recommended	not recommended		no data available	no data available
sofosbuvir/ ledipasvir		no data; coadministration not recommended		adjust/ monitor	if used with TDF, monitor for renal toxicity	if used with TDF, monitor for renal toxicity			
paritaprevir/ombitasvir/r +/- dasabuvir	contra-indicated	contra-indicated			contra-indicated	contra-indicated			
grazoprevir/ elbasvir	contra-indicated	contra-indicated			contra-indicated	contra-indicated			
ribavirin								contra-indicated	

* = component of WHO-recommended first-line HIV treatment. Green cells = can be co-administered; red cells = contraindicated; yellow cells = dose adjustment or toxicity monitoring recommended.

Interactions between DAAs and oral contraception

There is limited information on the safety of using DAAs during pregnancy; Annex 5 summarizes the information provided in package inserts approved by the EMA and the USFDA. The annex also indicates whether DAAs can be used with hormonal contraction.

DAAs and HBV/HCV coinfection

People with HBV/HCV coinfection were excluded from the clinical trials for DAAs. Consequently, there was no information on the safety of DAAs in persons with previously dormant HBV until DAAs were approved.

There have recently been a few reports of potentially life-threatening hepatitis B reactivation during HCV treatment. Although the reason for this reactivation is not known, it may be happening because the hepatitis C virus usually suppresses the hepatitis B virus [109, 110]. DAAs cause hepatitis C viral load to decline rapidly but are not effective against hepatitis B; this may create an opportunity for an abrupt increase in hepatitis B replication that can, in some cases, result in liver failure. Nevertheless, according to some experts, such flare-ups are clinically relevant only in a limited number of cases [*110 –112*].

These reports have prompted WHO, AASLD/IDSA and EASL, as well as regulatory agencies in the European Union, the USA and other countries, to issue warnings about the risk of HBV reactivation, and to stress that all patients should undergo HBV screening before starting HCV treatment. Patients should be monitored for HBV flare-ups or reactivation during treatment and post-treatment follow-up. HBV treatment should be provided if indicated.

DAAs and TB/HCV coinfection

In view of the hepatotoxicity of TB medicines and drug-drug interactions, simultaneous treatment of TB and HCV should be avoided. Active TB should usually be treated before commencing therapy for HCV [*5*].

Resistance, treatment failure and retreatment

Although DAAs are highly effective, the rate of treatment failure ranges from 1% to 15%, and up to half of people who were not cured may have resistance to one or more DAA classes [*113, 114*]. Thus, it is of note that nearly all approved and experimental HCV regimens include an NS5A inhibitor. NS5A inhibitors are potent and pan-genotypic, but have a low resistance barrier. Certain resistance-associated variants significantly reduce efficacy of NS5A inhibitors in treatment-naïve persons, especially if they have cirrhosis [*115*]. After HCV treatment failure, NS5A resistance-associated substitutions can persist for three years or longer [*116–118*].

More information about prevalence, geographical distribution and clinical impact of NS5A resistance-associated variants across HCV genotypes is needed to optimize treatment. To date, information on retreatment strategies is limited. Sponsors report resistance differently, making it difficult to compare across regimens and trials. Retreatment studies are small, reflecting high cure rates. Participants are often recruited from clinical trials but their complete data – including the initial regimen (or regimens) and duration, results from post-treatment failure resistance-testing (if performed) and liver disease staging – are not always available.

Given the ubiquity of NS5A inhibitors and the persistence of NS5A resistance, the most common strategy is to use a new DAA class (or a multiclass regimen), recycle SOF (if it was part of the initial regimen), add RBV and extend treatment duration to 24 weeks [*113*]. For example, in a study of 69 people with HCV genotype 1, 2 or 3 who were not cured by 4, 6, 8 or 12 weeks of SOF/VEL ± RBV or SOF/VEL/VOX, retreatment with 24 weeks of SOF/VEL + RBV cured 91% (63/69) overall. It is to be noted that cure rates were lowest in genotype 3 (78%, or 14/18) [*119*].

The phase II C-SURGE trial studied 16 weeks of MK-3682-B (a triple class regimen) with RBV, or 24 weeks without RBV, in 94 DAA-experienced people who had HCV genotype 1, with or without cirrhosis. An interim analysis reported 100% cure rates in 73 persons who reached 8 weeks post-treatment [*120*]. For more information on retreatment results, see Annex 6.

Paediatric patients

The rate of mother-to-infant HCV transmission is around 3–9%, and HCV prevalence among children ranges from 0.05% to 5% with significant geographical variation [*121*]. There are no interventions to eliminate the risk of mother-to-infant HCV transmission other than treating –and curing – women of childbearing age. However, DAAs have not been studied during pregnancy, and therefore it is not known whether it is safe to use them during pregnancy (see Annex 5 for more details).

Although hepatitis C usually progresses slowly in children [*122*], it is not always benign [*123*]. Liver disease progresses with duration of infection [*124*] and is more aggressive in paediatric chemotherapy patients and people who survived childhood cancer [*125*].

The DAAs currently on the market have not been approved for use in children or adolescents below 18 years of age. Some paediatric DAA treatment trials are ongoing (see Table 7); however, none of the regimens being studied are pan-genotypic. Results are available from a phase II trial of SOF/LDV in adolescents aged 12–17 years treated with adult dose SOF/LDV (400 mg/90 mg QD) for 12 weeks. Study participants were mostly Caucasian, treatment-naïve and non-cirrhotic; 63% were female. Ultimately, 98% (98 of 100) were cured – the remaining two participants were lost to follow-up. The most common adverse events were headache, fatigue and diarrhoea; all were mild or moderate [*126*].

TABLE 7.

Ongoing paediatric HCV treatment trials [127–130]

Regimen	Trial phase (sponsor)	Population	Sample size
Paritaprevir/ombitasvir/r ± dasabuvir, ± RBV	Phase II (AbbVie)	Ages 3–17 years Genotypes 1 and 4, with or without cirrhosis	N = 74
SOF/LDV	Phase II (Gilead Sciences)	Ages 12–17 years Genotypes 1 and 4; undergoing maintenance chemotherapy for haematological cancer	N = 40
SOF/LDV	Phase II (Gilead Sciences)	Ages 3–17 years Genotypes 1, 4, 5, 6 (genotype 3 + RBV, single site only) with or without cirrhosis, treatment-naïve or - experienced	N = 200
SOF/RBV	Phase II (Gilead Sciences)	Ages 3–17 years Genotype 2 or 3, treatment-naïve	N = 100

A pilot study on the safety and efficacy of 12 weeks of treatment with SOF+DCV in adolescents aged between 15 and 17 years has been conducted in Egypt. RBV was added for participants with cirrhosis. The study found this regimen to be safe and efficacious (100% SVR, N = 13) [*131*].

The pipeline (phase II/III): new strategies, new regimens

While a significant number of new DAAs has been launched in the past few years, others are still in the pipeline (see Figure 14 and Annex 7). As companies are increasingly developing regimens rather than single-component products, discussion in this section also focuses on regimens rather than individual DAAs. Moreover, it is limited to regimens currently in phases II/III.

The pipeline contains dual as well as triple DAA combinations. The strategy behind combining DAAs from three different classes (usually a nucleotide polymerase inhibitor, an NS5A inhibitor and a protease inhibitor) into fixed-dose "triplet" regimens is to cure more people faster. Trials have looked at 3, 4 and 6 weeks of treatment with 2-, 3- or 4-class regimens, with or without RBV. These trials have either involved a selected group of people with favourable prognostic factors or have reported suboptimal SVR rates [*132–136*]. Generally, 8 weeks seems to be the minimum duration for triple regimens; shorter treatment is unlikely to cure people with cirrhosis, especially if they are treatment-experienced.

Adding a third drug does not always boost cure rates, compared to a dual regimen – see for example SOF/VEL/VOX (discussed above). The other merits of a triple-class DAA regimen are unclear. A third drug increases the likelihood of drug–drug interactions and side-effects – possibly without significantly increasing efficacy. Also, it may cost more to treat people with three drugs for 8 weeks than with two drugs for 12 weeks. Finally, it is not clear whether it will be more difficult – or possible – to successfully re-treat persons who were not cured by a triple regimen.

Three pipeline regimens are discussed below; see Annex 8 for more detailed information.

Uprifosbuvir+ ruzasvir + grazoprevir

The once-daily, triple-class combination of uprifosbuvir (or MK-3682, a nucleotide polymerase inhibitor), ruzasvir (an NS5A inhibitor) and grazoprevir (an HCV protease inhibitor), is known as MK-3. In Part B of the phase II C-CREST trial, MK-3 was studied with or without RBV in treatment-naïve people with HCV genotypes 1 and 2, with and without cirrhosis, and in treatment-naïve and treatment-experienced people with genotype 3. The trial also included HIV-positive persons. In all genotypes, cure rates were higher with 12 weeks of treatment (97–100%) versus 8 weeks (86–95%) [*137*]. In Part C, 24 non-cirrhotic people who were not cured by 8 weeks of MK-3 in Part A of C-CREST, were retreated

with 16 weeks of MK-3 and RBV. All but one persons, who discontinued because of drug-related serious adverse events (abnormal heartbeat and vomiting), obtained SVR [*138*].

Another phase II trial, C-SURGE, is studying different durations of treatment with this regimen, with or without ribavirin, in DAA-experienced people with HCV genotype 1 (see the section on retreatment).

Odalasvir + AL-335 + SIM

Odalasvir (an NS5A inhibitor) and AL-335 (a nucleoside polymerase inhibitor) have been studied with or without simeprevir for 6 or 8 weeks in an 80-person, phase IIa trial. All participants had HCV genotype 1 and were treatment-naïve and non-cirrhotic. The four-arm trial compared doses of AL-335 (400 mg versus 800 mg) with 50 mg of odalasvir, either once daily or every other day, with or without 75 mg simeprevir. In persons treated for 8 weeks with the dual combination AL-335 and odalasvir, SVR was 90%. The triple-drug combination cured 100%, regardless of dose or duration. One adverse event, a cardiac abnormality, was considered probably related to odalasvir, and possibly related to AL-335 and SIM [*134*].

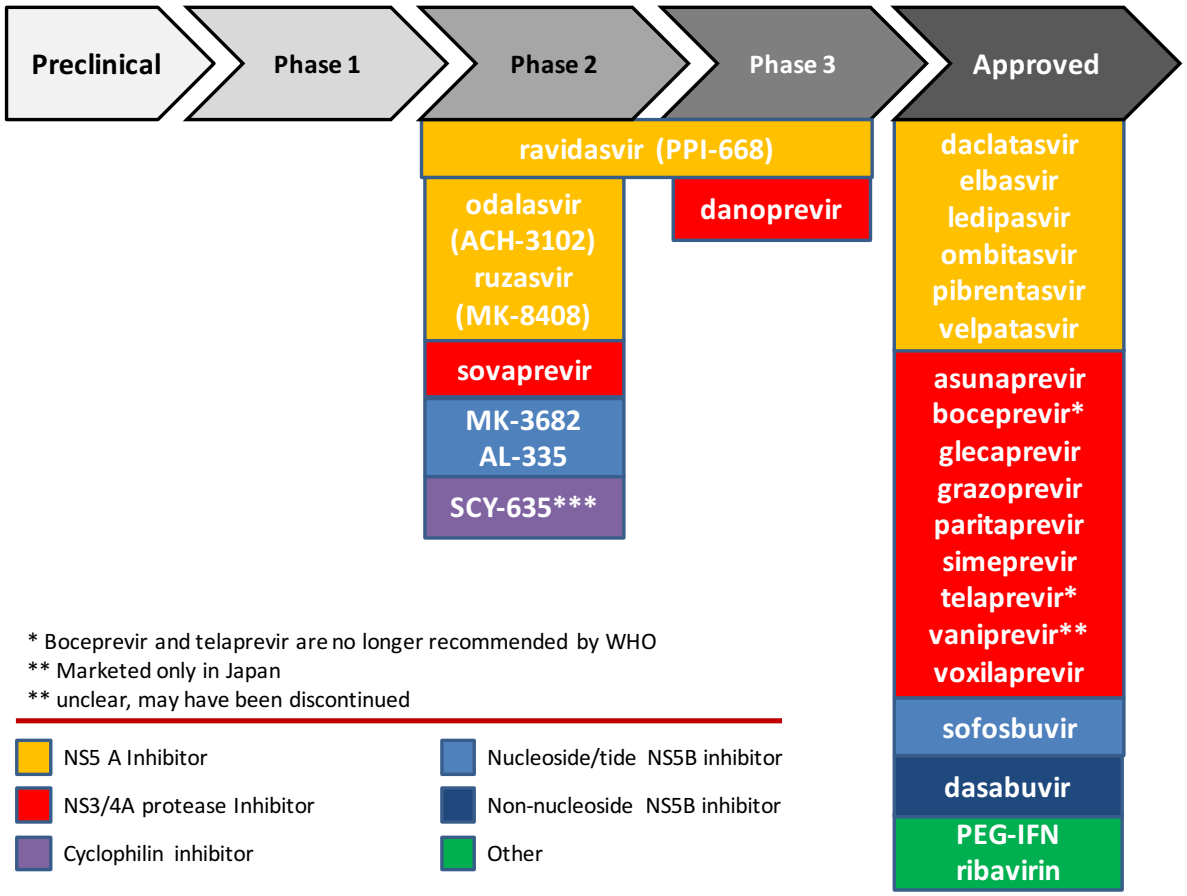
The triple combination is also being studied in genotype 3, in people with and without compensated cirrhosis. OMEGA-1 is an ongoing phase IIb trial comparing 6 versus 8 weeks of the once-daily regimen of odalasvir (25 mg) with AL-335 (800 mg) and SIM (75 mg) in 300 treatment-naïve, non-cirrhotic people with HCV genotypes 1, 2, 4, 5 and 6.

Sofosbuvir + ravidasvir

During a phase III trial in Egypt, 12-week treatment with the combination SOF + ravidasvir (an NS5A inhibitor) resulted in cure rates of 98% (N = 287) for HCV genotype 4. In non-cirrhotic patients the cure rate was 100% (N = 167) [*139, 140*]. Currently, the Drugs for Neglected Diseases Initiative (DNDi) is conducting phase II/III trials in Malaysia to assess the efficacy and safety of SOF + ravidasvir across all genotypes [*141, 142*]. The trial is open to all HCV genotypes, to persons with or without compensated cirrhosis, who are treatment-naïve or Peg-IFN/RBV-experienced, and/or HIV coinfected, and/or people who inject drugs. Persons without cirrhosis will be treated for 12 weeks; and duration is extended to 24 weeks for people with cirrhosis. As of June 15th 2017, 301 participants have been recruited; it is anticipated that the stage 1 study results will be available in December 2017.

DNDi intends to conduct additional clinical trials and prospective cohort studies in cooperation with the governments of Thailand and Malaysia, FIND, Médecins Sans Frontières, Oxford University, and civil society groups, and with Pharco/Presidio as industrial partners. The aim will be to assess the safety, efficacy and pharmacokinetics of SOF + ravidasvir across all genotypes. Special attention will be paid to the needs of key populations, including people who inject drugs (who do or do not receive oral substitution therapy), people living with HIV (to assess for possible interactions with commonly use antiretrovirals), and people with advanced liver or renal disease related to HCV. If successful, these trials will contribute to DNDi's objective of developing a highly efficacious, simple and affordable cure for HCV that will enable countries to implement a public health approach to hepatitis C [*143*].

FIGURE 14.
OVERVIEW OF HCV MEDICINES ON THE MARKET AND IN THE PIPELINE (PHASES II & III)



Source: Unitaid.

5. Market landscape

This chapter describes the market for DAAs. It examines both challenges associated with ensuring a robust supply of HCV drugs and market forces affecting the procurement and uptake of these medicines.

The market for DAAs is still relatively new or nascent in all parts of the world – particularly in low- and middle-income countries. Generic DAAs have been launched and prices have decreased – in some cases considerably. In other countries, DAAs are still expensive – notably in countries where there are patents and no licences. Volumes have increased rapidly but are still low. Demand and uptake are fluctuating, while financing remains insufficient or non-existent. The market for DAAs, therefore, though having taken off and holding great promise, is facing an uncertain future.

Market for existing products

This section summarizes key market data, as well as issues relevant for the production of generic DAAs. As Chapter 4 shows, SOF is a component of the most important treatments available to date. This chapter therefore focuses mostly on SOF and SOF-based regimens.

1. Regulatory approval

In the four years between August 2013 and August 2017, five new single-component DAAs and six new FDCs received their first regulatory approval.[11] Table 8 provides an overview of the registration dates of those new DAAs (originator product) as of 31 July 2017, in as far as data are available on the websites of national regulatory authorities, originator companies or the Martindale [*144*]. Table 9 indicates where generic versions of some of the key DAAs are registered.

[11] Boceprevir and telaprevir were the first DAAs to receive marketing approval. However, they are no longer recommended by WHO [5], and are not discussed in this section.

TABLE 8.

Overview of registration date of DAAS by originators (as of 31 July 2017)

	simeprevir	sofosbuvir	asunaprevir	daclatasvir	vaniprevir*	sofosbuvir/ ledipasvir (FDC)	dasabuvir	ombitasvir/ paritaprevir (FDC with ritonavir)	grazoprevir/ elbasvir (FDC)	sofosbuvir/ velpatasvir (FDC)	sofosbuvir/ velpatasvir/ voxilaprevir (FDC)	glecaprevir/ pibrentasvir (FDC)
Australia	18 July 2014	19 July 2014	25 May 2015	25 June 2015	--	13 May 2015	10 July 2015	10 July 2015	29 Aug 2016	19 Dec 2016	--	--
Argentina	20 May 2015	30 Oct 2015	--	09 Apr 2015	--	30 Aug 2016	20 Nov 2015	20-Nov 2015	--	June 2017		
Bolivia		Dec 2015			--	Dec 2016						
Brazil	11 Mar 2015	30 Mar 2015		6 Jan 2015	--	--	23 Apr 2015	23 Apr 2015		--		
Cameroon		June 2016				May 2016						
Canada	18 Nov 2013	13 Dec 2013	09 Mar 2016	13 Aug 2015	--	15 Oct 2014	22 Dec 2014	22 Dec 2014	19 Jan 2016	11 July 2016	--	--
Chile		Apr 2015	June 2015	7 July 2016	--	July 2016	30 Aug 2016	30 Aug 2016		--		
China	--	--	24 Apr 2017	24 Apr 2017	--	--	--	--	--	--	--	
Colombia	21 July 2015	May 2017	27 July 2015	27 July 2015	--	--	25 Jan 2016	25 Jan 2016	--	--	--	
Costa Rica						Aug 2016						
Dominican Republic		July 2015			--	Nov 2016				--		
Ecuador		Nov 2016				--						
Egypt	--	10 July 2014	--	5 Aug 2015	--	15 Nov 2015	--	--	7 Dec 2016	--	--	
El Salvador		Dec 2015			--	Aug 2016						
Ethiopia		--			--	Dec 2015						
European Union	14 May 2014	16 Jan 2014	--	22 Aug 2014	--	17 Nov 2014	15 Jan 2015	15 Jan 2015	22 July 2016	6 July 2016	28 July 2017	28 July 2017
Georgia		Feb 2015			--	July 2015				Oct 2016		
Hong Kong,SAR China	26 Oct 2016	2 Mar 2015	13 May 2016	13 May 2016	--	7 Aug 2015	20 May 2015	20 May 2015	--	--		
India	--	13 Jan 2015	--	14 Dec 2015	--	June 2017	--	--	--	--		
Indonesia	29 Aug 2016	30 June 2016	--	--	--	--	--	--	--	--	--	
Iran (Islamic Republic of)**		Yes							Yes			

	simeprevir	sofosbuvir	asunaprevir	daclatasvir	vaniprevir*	sofosbuvir/ ledipasvir (FDC)	dasabuvir	ombitasvir/ paritaprevir (FDC with ritonavir)	grazoprevir/ elbasvir (FDC)	sofosbuvir/ velpatasvir (FDC)	sofosbuvir/ velpatasvir/ voxilaprevir (FDC)	glecaprevir/ pibrentasvir (FDC)
Japan[x]	27 Sep 2013	26 Mar 2015	4 July 2014	4 July 2014	26 Sep 2014	3 July 2015	--	28 Sep 2015	--	--	--	--
Lebanon		Yes		Yes		Yes	Yes	Yes		Yes		
Malaysia	--	(Sep) 2015	--	(Apr) 2016	--	(Mar) 2016	(June) 2015	(June) 2015	--	--	--	
Mauritius						Jan 2017						
Mexico	16 June 2014	17 Dec 2015	29 Oct 2015	5 Oct 2015	--	08 Feb 2016	9 Dec 2016	9 Dec 2015	18 Nov 2016	8 Jun 2017	--	
Mongolia		Jan 2015			--	May 2015						
Morocco		--			--	May 2016						
Nigeria		June 2016				--						
New Zealand	3 Sep 2015	20 mar 2014	30 Jun 2016	30 Jun 2016	--	06 nov 2014	20 Aug 2015	20 Aug 2015	1 Dec 2016	10 Nov 2016	--	
Norway	1 July 2014	15 Mar 2014	--	01 Nov 2014	--	15 Jan 2015	15 Mar 2015	15 Mar 2015	1 Dec 2016	15 Aug 2016	--	
Pakistan		feb 2015			--	--				--		
Peru		May 2016			--	Jan 2017						
Philippines	--	1 Oct 2015	--	--	--	25 May 2017	--	--	--	--	--	
Qatar				16 Sep 2015			26 Mar 2015	26 Mar 2015				
Russian Federation	27 Feb 2014	(Q1-2) 2016	3 June 2015	14 July 2015	--	--	21 Apr 2015	21 Apr 2015				
Rwanda		Aug 2015			--	Aug 2015						
Saudi Arabia	2014	2014	--	2015	--	2015	2015	2015	(Q3) 2016	--	--	
South Africa**	--	--	--	--	--	--	--	--	--	--	--	
Switzerland	04 Mar 2015	18 Mar 2014	--	26 Jun 2015	--	16 Dec 2014	25 Nov 2014	25 Nov 2014	01 Apr 2016	22 Sep 2016	--	--

	simeprevir	sofosbuvir	asunaprevir	daclatasvir	vaniprevir*	sofosbuvir/ ledipasvir (FDC)	dasabuvir	ombitasvir/ paritaprevir (FDC with ritonavir)	grazoprevir/ elbasvir (FDC)	sofosbuvir/ velpatasvir (FDC)	sofosbuvir/ velpatasvir/ voxilaprevir (FDC)	glecaprevir/ pibrentasvir (FDC)
Thailand		Aug 2015		Yes**	--	Sep 2016				--		
Turkey	Yes	Yes			--	Yes	Yes	Yes				
Tunisia	--	28 Jan 2016	--	Yes	--	Jan 2016	28 Jan 2016	28 Jan 2016	--	--	--	
Ukraine		Oct 2015				Mar 2017						
United Arab Emirates**	--	--	--	--	--	--	--	Yes	--	--		
United Republic of Tanzania		Dec 2016				Oct 2016						
Uruguay		Mar 2016			--	Apr 2016						
Uzbekistan		Oct 2016				--						
Venezuela		July 2016			--	--						
USA	22 Nov 2013	6 Dec 2013	--	24 Jul 2015	--	10 Oct 2014	19 Dec 2014	19 Dec 2014	28 Jan 2016	28 Jun 2016	18 July 2017	--
Zimbabwe	--	--	--	--	--	--	--	--	--	--		

Notes: -- indicates the product was not registered as of 31 July 2017. A blank means no information is available. Date of first worldwide registration is underlined. FDC = fixed-dose combination.

* Merck has announced that vaniprevir will be made available only in Japan [*145*].

** Information as of 28 February 2017.

x Data available until 31 December 2016

TABLE 9.

Overview of registration of generic DAAs (as of 31 July 2017)

	DCV	SOF	SOF/DCV	SOF/LDV	SOF/VEL
Bangladesh	yes	yes	yes	yes	yes
Bhutan		yes		yes	
Cambodia	yes	yes		yes	yes
Chad	yes	yes		yes	
Congo (Republic of)		yes			
Egypt	yes	yes		yes	
El Salvador		yes		yes	
Ethiopia		yes			
Gabon	yes	yes		yes	
Guatemala		yes			
India	yes	yes		yes	yes
Indonesia		yes			
Iran (Islamic Republic of)	yes	yes	yes	yes	
Ivory Coast		yes		yes	
Kazakhstan		yes			
Kyrgyzstan	yes	yes		yes	
Malawi		yes			
Mongolia		yes		yes	
Mozambique		yes			
Myanmar	yes	yes		yes	yes
Nepal	yes	yes		yes	yes
Nicaragua		yes			
Pakistan		yes			
Sri Lanka		yes			
Turkmenistan	yes	yes		yes	
Uganda		yes			
Uzbekistan	yes	yes		yes	

Sources of data: [*144, 146, 147*] and Annex 13. A blank means no information is available.

National registration may be facilitated (depending on national authorities and regulations) if a medicine has been prequalified by WHO. Table 10 provides an overview of DAAs that are prequalified or that have been approved by the Expert Review Panel[12] as of 31 July 2017. Several generic versions of SOF are in the process for prequalification.

[12] The Expert Review Panel (ERP) is a group of independent experts who review the potential risks and benefits associated with the procurement and use of a pharmaceutical product that may have high public health impact but that has not yet undergone a stringent assessment, either by the WHO prequalification programme or by a stringent regulatory agency. Products approved by the ERP can be procured through The Global Fund. The ERP provides an interim solution for a time-limited period, in anticipation of the completion of a stringent review process.

TABLE 10.

Overview of WHO prequalified DAAs (31 July 2017)

Product	WHO-prequalified		Expert Review Panel approved*	
	Date	Company	Date	Company
Finished products				
DCV	October 2016	Bristol-Myers Squibb (originator product)	--	--
SOF	--	--	October 2016	Hetero
SOF	July 2017	Mylan	October 2016	Mylan
SOF	--	--	June 2017	Pharco
Active pharmaceutical ingredients (API)				
SOF API	February 2017	Mylan	--	--

* See footnote 12.

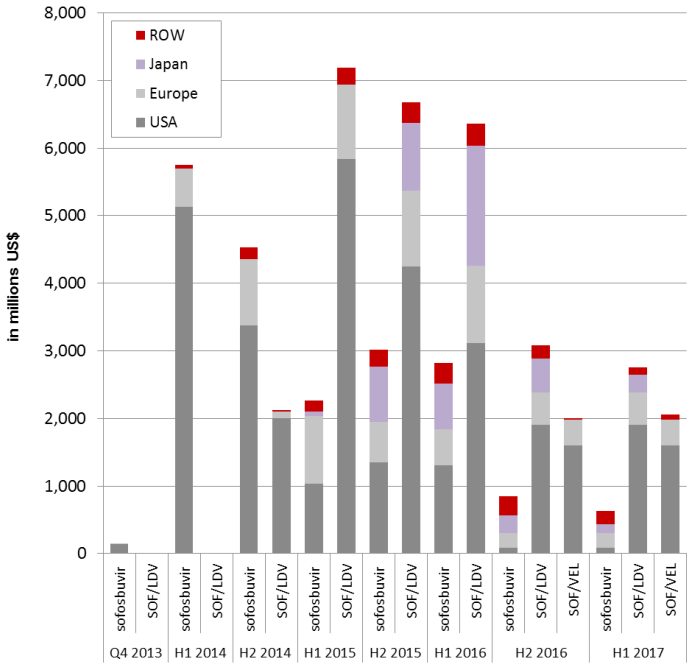
2. Sales to date

Several DAAs became "blockbuster medicines" (medicines that achieve annual global revenues of over US$ 1 billion [*148*]) within months of their first global launch. In some instances, they were rapidly replaced by better, newer DAAs. In particular, SOF became a record-breaking new medicine in terms of sales [*149*] – and was subsequently surpassed by the combination SOF/LDV (see Table 11 and Figure 15).

In the three years 2014–2016, worldwide originator sales of SOF and SOF-based FDCs have surpassed US$ 46 billion. The majority of these sales (~95% by value) took place in high-income countries (see Annex 9).

FIGURE 15.

GLOBAL ORIGINATOR SALES OF SOF, SOF/LDV AND SOF/VEL, BY HALF-YEAR



Notes: H1 = 1st half of the year (January–June); H2 = 2nd half of the year (July–December).
ROW = Rest of the world. ROW sales were mainly in Canada, Egypt and Pakistan (2014–2015), and in Australia, Brazil, Egypt and Canada (2016).
Source of data: Gilead. 2017 sales in Japan were estimated by Unitaid.

TABLE 11.

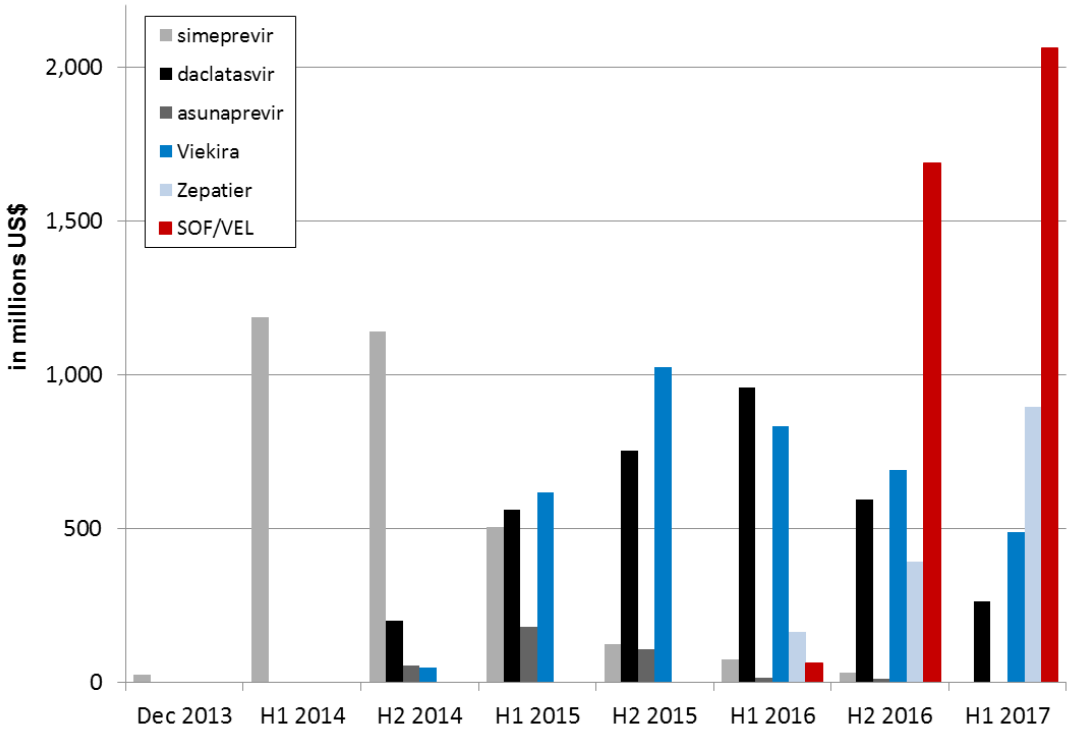
Global originator sales of SOF and SOF-based FDCs (US$ 000s), by year

	SOF	SOF/LDV	SOF/VEL	Total
2013	139 000	--	--	**139 000**
2014	10 283 000	2 127 000	--	**12 410 000**
2015	5 240 000	13 864 000	--	**19 104 000**
2016	4 001 000	9 081 000	1 752 000	**14 834 000**
Total	**19 663 000**	**25 072 000**	**1 752 000**	**46 487 000**

Source: Gilead. For more details, see Annex 9

Originator sales of the other DAAs launched between December 2013 and March 2016 are summarized in Table 12 and Figure 16. For more details, see Annex 9.

FIGURE 16.
GLOBAL ORIGINATOR SALES OF SELECTED DAAS, BY HALF-YEAR



Notes: H1 = 1st half of the year (January–June); H2 = 2nd half of the year (July–December).
Source of data: AbbVie, Bristol-Myers Squibb, Johnson & Johnson, Medivir and Merck.

TABLE 12.

Global originator sales of selected DAAs (US$ 000s), by year

	asunaprevir	DCV	SIM	Viekira®	GZR/ELB	Total
2013	--	--	23 000	--	--	**23 000**
2014	55 000	201 000	2 328 000	48 000	--	**2 632 000**
2015	288 000	1 315 000	627 000	1 639 000	--	**3 869 000**
2016	28 000	1 550 000	106 000	1 522 000	555 000	**3 761 000**
Total	**371 000**	**3 066 000**	**3 084 000**	**3 209 000**	**555 000**	**10 285 000**

Source: AbbVie, Bristol-Myers Squibb, Johnson & Johnson Medivir and Merck.
For more details, see Annex 9

The emergence of the highly effective DAAs has resulted in a substantial expansion of the global market for HCV medicines. In 2016, the DAAs accounted together for more than US$ 18.5 billion in sales – more than three times the total market value of HCV drugs in 2012, which amounted to around US$ 5 billion (Peg-IFN and RBV together represented US$ 3.5 billion in purchases in 2012, with boceprevir and telaprevir accounting for the remainder).[13]

3. Originator market dynamics/prices

The very high prices for new DAAs contribute to the extraordinary level of sales they have generated. In the USA, SOF was launched at a price of US$ 1000 a pill, or US$ 84 000 for 12 weeks of treatment. SOF/LDV was launched at US$ 94 500 for a 12-week course.[14] Other DAAs are also launched with very high prices.

High-income countries

In high-income countries, health advocates and patients' groups have decried the high price of Sovaldi® [*150*], and administrators of public-sector health programmes (e.g., Medicare and Medicaid in the USA) have warned that the price of SOF threatens to place severe financial strains on their programmes and have placed restrictions on access [*151*]. In 2014, the United States Senate launched an investigation into the price of Sovaldi® [*152*].

[13] Merck, Roche and Vertex 10K reports.
[14] Note: these prices are the list prices/prices at product launch. Lower prices have since been reported on the basis of negotiated agreements with insurance companies, but these are generally confidential.

Some high-income countries have limited coverage of SOF with public-sector funds because of its high price (e.g. prioritizing persons with advanced or symptomatic infection) [*153–157*].

Public criticism, price negotiations by governments and insurance companies and competition from alternative regimens have brought prices down – though in most high-income countries DAAs are still very costly. In late 2015/early 2016, the median price for 12 weeks of SOF in 26 Organisation for Economic Co-operation and Development (OECD) countries was US$ 42 017 (ranging from US$ 37 729 in Japan to US$ 64 680 in the USA) [*158*].

A number of high-income countries have devised creative solutions to facilitate access to DAAs. Notably, in December 2015, the Australian Health Ministry announced a 5-year volume-based price deal that reportedly is based on treating an estimated 62 000 people for AUS$ 1 billion (this would represent a cost of ~AUS$ 16 130 – approximately US$ 11 700 – per person, if indeed 62 000 people are treated) [*159–161*]. The deal involves a cap on payment, and would enable the treatment of more people at the same cost, if they are identified. In the first year, over 38 000 people are reported to have been treated [*162*].

Meanwhile, in what has been called "an unprecedented move" [*163*], the medicines regulatory agency in Switzerland is exceptionally allowing importation for personal use of up to three months' supply of hepatitis C medicines (instead of the normal limit of one month's supply) [*163, 164*]. Additionally, one of the Swiss health insurance companies has announced it will refund part of the out-of-pocket costs to patients importing DAAs via a particular Australian buyers' club [*164–166*].

Italy, too, has changed its regulations to enable importation of medicines for personal use by patients who are not (yet) eligible for treatment in the national health system [*167*]. There are also reports that some countries in Europe may be considering compulsory licensing to lower the costs of hepatitis C medicines [*168, 169*].

Low- and middle-income countries

Originator prices are much lower in other countries. Notably, in May 2014, Egypt, the country with the highest HCV prevalence, concluded an agreement with Gilead to purchase a 12 weeks' course of SOF for US$ 900 [*170*].Gilead has since extended this price to the 101 low- and middle-income countries included in its voluntary licences (see section 5 below), and subsequently set the price of for SOF/LDV for these countries at US$ 1200 for 12 weeks [*171, 172*]. In September 2016, Gilead reduced

its prices to US$ 750 for 12 weeks of SOF and US$ 900 for 12 weeks of treatment with either SOF/LDV or SOF/VEL. Four additional countries (Armenia, Georgia, Moldova and Ukraine) are now eligible to procure at these prices [*173*].

Other middle-income countries are not eligible for these prices and pay much more. A 12-week treatment with SOF would cost over US$ 6000 in Argentina or Brazil [*153*]. In Malaysia, it would cost US$ 54 000 [*174*] – which is well above the average OECD price.

4. Cost of research and development

One of the frequently mentioned justifications for high prices of medicines is the high cost of research and development (R&D). As noted earlier, the high launch price of SOF attracted significant criticism but also scrutiny of Gilead's price-setting strategy and the R&D expenditures pertaining to SOF. Based on an investigation by the United States Senate, the most accurate – though high-end – estimate of SOF's R&D costs is US$ 942.7–1151.3 million [*175, 176*] (the higher estimate includes the costs of early research failures at Pharmasset, the company that initially developed SOF).[15]

The actual cost to Gilead was significantly higher – around US$ 12 billion – due to its US$ 11.2 billion "speculative acquisition" of Pharmasset [*176*].

A member of the United States Senate Committee on Finance that conducted the investigation into SOF's United States prices noted, however, that "there was no concrete evidence in emails, meeting minutes or presentations that basic financial matters such as R&D costs or the multi-billion dollar acquisition of Pharmasset, the drug's first developer, factored into how Gilead set the price" [*177*].

As of the end of 2016 (i.e. 3 years after it was first approved), Gilead's sales of SOF amounted to more than 16 times SOF's development costs and around 1.6 times Gilead's expenditures on SOF. These numbers do not include sales of other SOF-based products, such as SOF/LDV (with higher sales than SOF).

[15] Both numbers are high-end estimates as they include at least part of Gilead's expenditures on the development of other SOF-based medicines, such as SOF/LDV [*175*].

5. Patents and licences

Patents may be granted to inventions that are new, that are inventive (i.e. not obvious) and that are industrially applicable. A patent provides exclusive rights over an invention, generally for a period of 20 years from the date of application. During the patent term, the patent-holder may prevent others from making, importing or using the patented product in the country where the patent was granted. Patent protection precludes generic competition for the product; the lack of competition allows prices to remain high.

Medicines are usually subject to multiple patents which fall in several broad categories, notably:

- *The compound patent*, main or basic patent. Such patents cover the active ingredient and, where in force, completely block manufacture, import and use of generic versions – both the active pharmaceutical ingredient (API) as well as all finished pharmaceutical products.

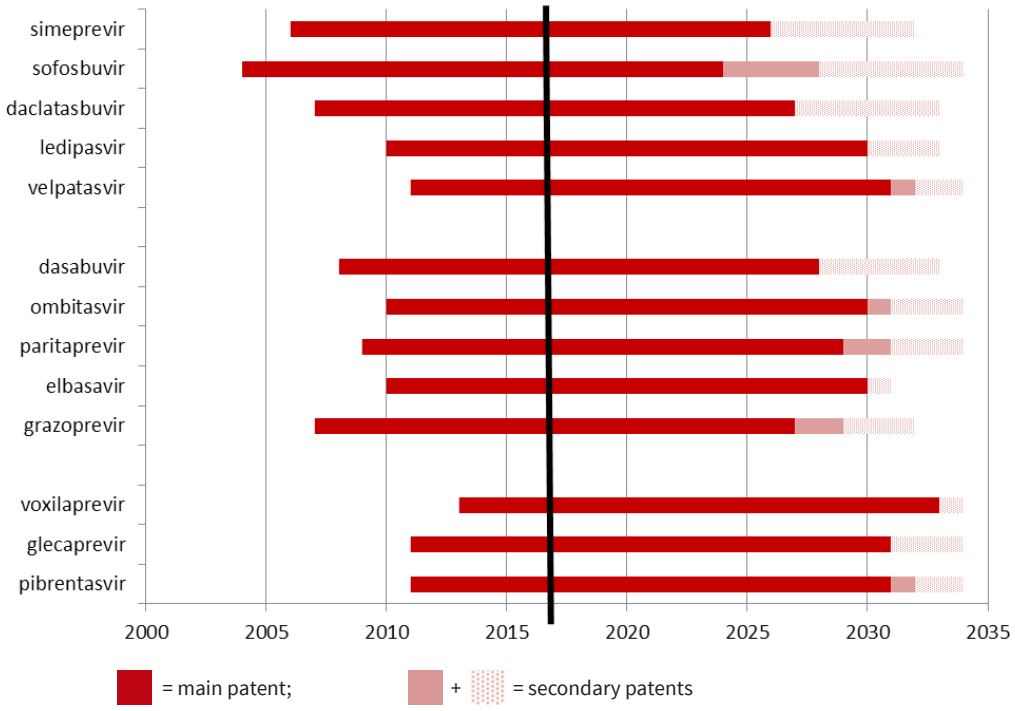
- *Process patents and patents on intermediates in the production process*. These may block manufacturing of generic products (usually the API), unless an alternative production method can be found that does not use the patented process or intermediates.

- *Formulation patents*. These secondary patents vary widely, and may cover a particular dosage form, dose, or form of the active ingredient. The ability of such patents to block generic competition varies.

Key patents on the new DAAs are likely to remain in force until after 2025, and additional patents may effectively extend the duration of patent protection (Figure 17). As far as is known, these patents have been filed or granted in many countries that have pharmaceutical manufacturing capacity. A summary of the available patent information can be found in Annex 10. The production of generic versions would, in principle, be delayed until after the expiry of the relevant patents.

FIGURE 17.

APPROXIMATE PATENT TERMS FOR SELECTED DAAS



Source of data: WHO [*51–55*], Unitaid [*178–183*].

There have been challenges to SOF patents. In February 2014, the patent office in Egypt rejected a patent application for SOF for lack of novelty and lack of inventiveness (though other patent applications are still believed to be pending). Not-for-profit organizations and generic companies have filed pre-grant oppositions to patent applications for SOF at the European Patent Office, as well as in Argentina, Brazil, China, India, the Russian Federation, Thailand and Ukraine [*55,184–187*]. As a result, the European Patent Office partially revoked[16] one of the SOF patents in October 2016 [*186–188*].

Access to new, patented medicines can be expanded through licences; a licence allows the importation, sale, use and/or production of generic versions of a patented medicine in the country or countries covered by the licence. Licences can be granted voluntarily by the patent-holder or they can be compulsory, in which case the licence is granted by a government authority without the consent of the patent-holder.

[16] A number of claims were rejected

Voluntary licences on sofosbuvir, ledipasvir and velpatasvir

In September 2014, Gilead signed voluntary licences for SOF and LDV with a number of major generic producers in India. As licence-holders, these companies have the right to manufacture generic versions of SOF and LDV, and supply them to the countries included in the licence. In January 2015, these licences were amended to include VEL [*189*].

Currently, 11 Indian generic manufacturers have signed these voluntary licences which cover 101 low- and middle-income countries [*190*]. These include a number of middle-income countries with significant numbers of people with HCV, such as Egypt and Indonesia (see Annex 11 for the complete list of countries). This may create sufficient demand to enable economies of scale. However, other middle-income countries with large numbers of people with HCV, such as Brazil and China, are not included in the voluntary licence.

Voluntary licences on NS5A inhibitors daclatasvir and ravidasvir

In November 2015, Bristol-Myers Squibb signed a voluntary licence with the Medicines Patent Pool for DCV. The licence covers 112 countries (all low-income countries and least-developed countries, as well as over 70 middle-income countries) (see Annex 11). Currently, 10 generic manufacturers have signed a sublicence for DCV.

In November 2014, the Egyptian company Pharco signed a licence for a pipeline NS5A inhibitor, ravidasvir (or PPI-668) for Egypt [*191*]. In March 2016, DNDi signed a non-exclusive licence for ravidasvir for 21 low- and middle-income countries, including a number of large middle-income countries that are often not included in voluntary licences (such as Brazil, Colombia, Mexico, South Africa and Thailand). In April 2017, the Medicines Patent Pool obtained a licence for ravidasvir covering a number of additional middle-income countries (including Russia, most of North-Africa and the Middle-East, and some central/eastern European countries). In many other countries – such as in most of sub-Saharan Africa – there are no patents on ravidasvir (and hence there is no need for a licence). DNDi furthermore has the option to obtain, after 21 March 2018, a non-exclusive licence for ravidasvir for 40 high-income countries. DNDi, Pharco and Presidio have also agreed to supply the combination of SOF and ravidasvir, once approved, at a price of US$ 294 or less per treatment course [*143*].

6. Generic direct-acting antivirals: availability and prices

Countries included in the voluntary licences can procure generics from the licence-holders (regardless of whether the medicine is patented in the country). For daclatasvir, countries that are not in the licence, but where no patent has been granted, can also buy generics from licence-holders.[17] The situation is more complex for countries that are not included in Gilead's voluntary licence (see Annex 12).

When no patents have been granted, countries can also opt to buy generics produced by manufacturers that do not hold a licence. For instance, pharmaceutical companies in Bangladesh or Egypt do not need a voluntary licence. In Bangladesh, patents for these DAAs have not been filed[18] [*55, 192*]. In Egypt, key patents for SOF have either not been filed or have been rejected.

Generic versions of SOF, SOF/LDV and DCV are already available from multiple manufacturers in Bangladesh, Egypt and India (see Annex 13). Generic manufacturers are also developing, or already marketing, FDCs combining DAAs from different originators, such as SOF/DCV [193] (see also Annex 13). Reportedly, locally-produced generic DAAs are also being developed and are becoming available in other countries, such as Argentina and Morocco [*153, 194*].

Generic prices of SOF and SOF/LDV have de facto been capped by Gilead's announced access prices but quickly fell well below those levels. Notably, prices of generic versions of SOF have decreased rapidly (see Table 13). Prices of generic daclatasvir have been relatively modest from the start. Some of the lowest prices for have been obtained through a tender by the Government of Punjab [*195*].

[17] Provided the licence-holder does not rely on the originator's technology.

[18] In addition, under World Trade Organization rules, Bangladesh, as a least-developed country, is not obliged to implement or enforce patent rights (see the Doha Declaration on the TRIPS Agreement and Public Health, paragraph 7).

TABLE 13.

Lowest reported generic prices (in US$, for 12 weeks)

	Q2 2015 (India)	Q4 2015 (India)	Q1 2016 (India)	Q4 2016–Q1 2017	
				(Egypt)	(India)
DCV	--	--	$ 183	$ 21	$ 39
SOF	$ 750	$ 513	$ 325	$ 153	$ 66
SOF/LDV	--	--	$ 615	--	$ 191

Q=Quarter (year).
Source: [*153, 195, 196*].

As can be seen from Table 13, a 12-week cure (SOF + DCV) for HCV can be obtained for less than US$ 200 from suppliers in Egypt and India.

7. Quality considerations

While the availability of affordable generic DAAs is key to increasing access and achieving the hepatitis C elimination targets, it is also crucial that the quality of the DAAs is assured; price reductions should not be achieved at the cost of compromising quality. Fierce price competition may, however, increase the risk of substandard products appearing on the market.

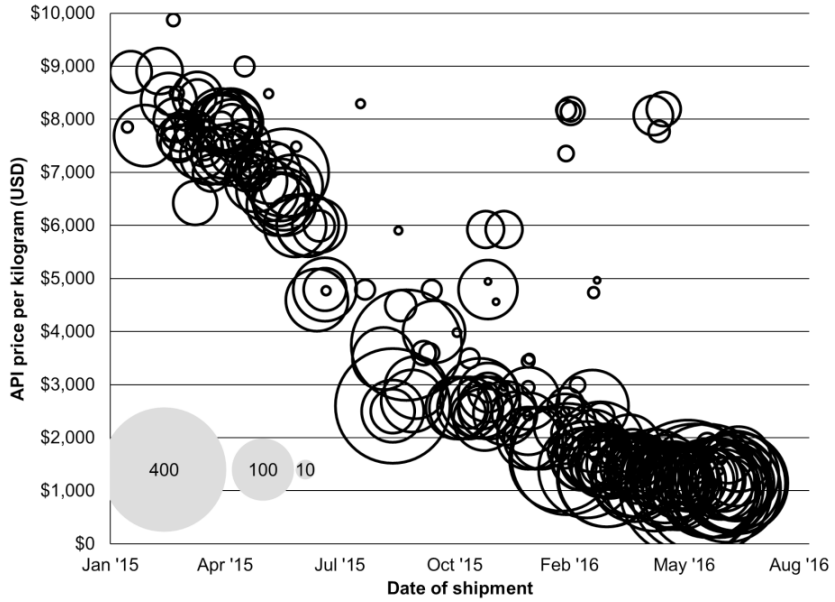
8. Production costs

DAAs for treatment of hepatitis C are similar in chemical structure and mode of action to ARVs – e.g. sofosbuvir is a nucleotide analogue like tenofovir. Therefore, it should be possible to produce DAAs at relatively low cost to enable the treatment of large numbers of people with HCV. The first estimates of the cost of production of DAAs were based on analysis of the routes of chemical synthesis [*197, 198*]. These analyses predicted that sofosbuvir could be manufactured for US$ 68–136 per 12-week treatment course, while daclatasvir could be produced for US$ 10–20 per 12-week treatment course [*197, 198*].

More recently, costs of production have been estimated on the basis of the average cost of the API exported from India; demand volume is a key determinant of API production costs [*199*].

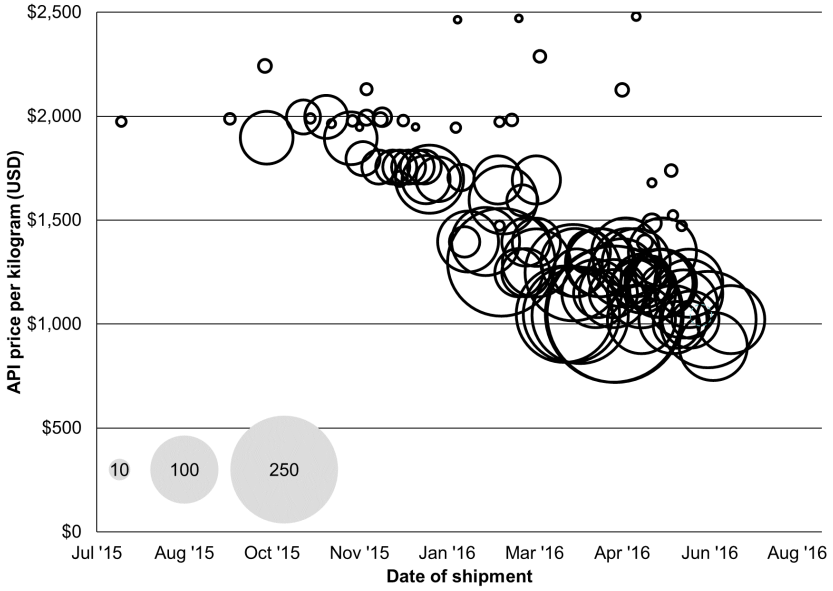
API export data of DCV, LDV and SOF were extracted from an online database of Indian export ledgers [*200*]. Volumes of SOF and DCV API exported from India have increased between January 2015 and July 2016, and prices have fallen significantly (see Figures 18 and 19).

FIGURE 18.
COSTS PER KILOGRAM OF SOFOSBUVIR API EXPORTED FROM INDIA, 2015–2016



Note: Each point represents a single shipment. The size of each point represents the number of kilograms of sofosbuvir exported.

FIGURE 19.
COSTS PER KILOGRAM OF DACLATASVIR API EXPORTED FROM INDIA, 2015–2016



Note: Each point represents a single shipment. The size of each point represents the number of kilograms of daclatasvir exported.

The prices of API for sofosbuvir and daclatasvir have fallen by 50– 80% in the past two years, as volumes of production have risen. If volumes of velpatasvir and ledipasvir API see a similar increase, their prices could also fall significantly over time.

On the basis of the above data, average API costs were calculated for 1 June 2016, using linear regression models weighted by the amount exported (see Table 14). Using the API cost per kilogram, the cost of production of finished pharmaceutical products (tablets) can be estimated, as shown in Figure 20. The calculation assumes large production volumes.

TABLE 14.

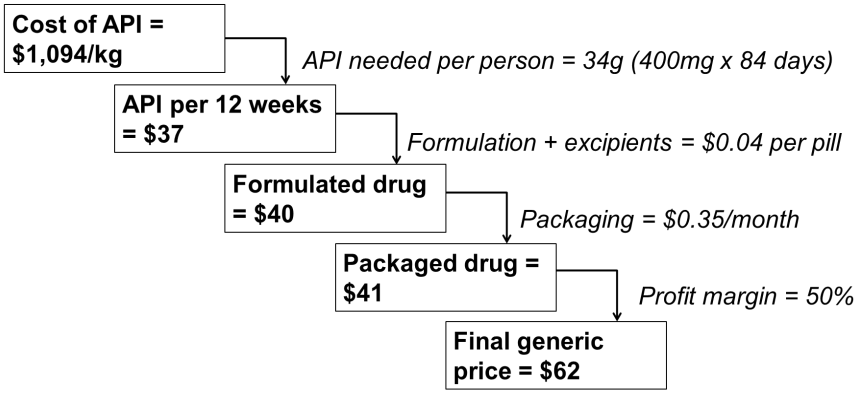
Volumes and prices of APIs for selected DAAs from India

	API exports in kg (January–June 2016)	Mean API prices in US$ (1 June 2016)
Daclatasvir	5443 kg	$ 998/kg
Ledipasvir	240 kg	$ 2441/kg
Sofosbuvir	10 200 kg	$ 1094/kg
Velpatsvir *	––	$ 8900–11 700/kg

* Note: The API cost of VEL was estimated on the basis of an analysis of the chemical synthesis processes described in the originator's patents (as export data are not yet available).

FIGURE 20.

ESTIMATED MINIMUM COST TO MANUFACTURE SOF, BASED ON API PRICES (US$)



Source: A. Hill.

Generic production costs for DCV, LDV and VEL were estimated in the same way; results are shown in Table 15. It should therefore be possible to manufacture a 12-week supply of sofosbuvir plus daclatasvir for US$ 76 per person.

TABLE 15.

Price range (US$) for selected DAAs, versus target prices

Product	API cost/kg (US$) (June 2016)	Target US$ price for 12-week treatment	Current lowest global US$ price for 12-week treatment*	Current US$ prices for 12-week treatment*
SOF	$ 1094	$ 62	$ 66	$ 49 860–84 000
DCV	$ 998	$ 14	$ 21	$ 50 653–63 000
LDV	$ 2441	$ 34	N/A	N/A
SOF/LDV	N/A	$ 96	$ 507	$ 56 700–94 500
VEL	$ 8900–11 700	$ 119–154	N/A	N/A
SOF/VEL	N/A	$ 181–216	--	$ 74 760

* Source of data: [153, 158, 195,196, 201, 202]. N/A = not applicable; -- = unknown.

The costs and prices of certain generic DAAs have fallen rapidly. In early 2015, the best price for SOF was US$ 900 per 12-week course of treatment. This price had fallen to US$ 153 in late 2016 (from Pharco in Egypt) [*153*] and to US$ 66 in early 2017 (tender by the Government of Punjab) [*195*]. Thus, generic SOF can already be obtained at prices close to the cost estimated above. Similarly, it may be possible that prices of other DAAs will also decrease further – closer to the cost estimates above – if order volumes become larger and more reliable.

Nevertheless, countries where the concerned products are patented but which are not included in the voluntary licences will not be able to obtain generics and will not be able to benefit from these low prices – unless they make use of "TRIPS flexibilities" such as compulsory licensing.

Access and volumes

The number of people that have been treated with DAAs is not known, but as most regimens contain SOF, the volume of SOF-based treatments can be used as a (low-end) marker for the number of people who have been able to access DAAs. This volume can be estimated based on market data.

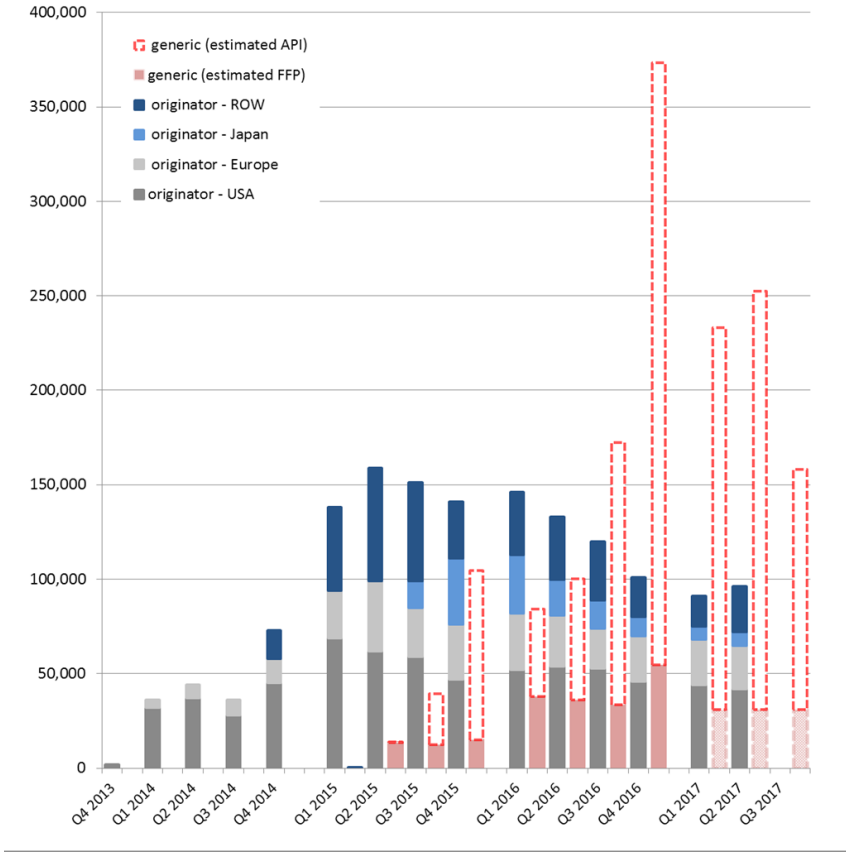
The number of people receiving treatment with SOF-based combinations from the originator is available [*203–206*]. The number of people who have been/can be treated with generic SOF or SOF-based regimens can be estimated based on i) data on SOF API exports from India[19], ii) data on SOF-containing finished products (tablets) exported from India, and iii) domestic consumption of SOF and SOF-containing FDCs in India [*200, 207, 208*]. The estimate would be a conservative or low-end estimate as it does not include SOF-containing medicines produced with API that does not originate from India.

Figure 21 and Table 16 compare a conservative estimate of the number of people who have been treated with generic SOF and SOF-containing medicines with the number of people treated with SOF and SOF-containing medicines produced by the originator.

[19] The amount of SOF API exported, divided by the amount of SOF API necessary for the production of one 12-week treatment course (which, including a 10% margin for production losses, is 37 g) provides an estimate of the number of treatments that can be produced.

FIGURE 21.

ESTIMATED NUMBER OF PEOPLE TREATED WITH SOF-CONTAINING REGIMENS, 2014 TO SECOND QUARTER 2017, BY QUARTER-YEAR (Q)



ROW = Rest of the world; FPP = finished pharmaceutical product.
Notes: Generic estimates are conservative/low-end estimates, as they do not include finished products (tablets) containing API produced outside India. See also footnote 19. Generic estimates are based on sales/exports of finished products (FFPs) from the previous quarter, or on API exports two quarters previously, to make them more comparable with originator sales (taking into account the time necessary for transport, production of the final dosage form and sale). Estimates/projections regarding generic FPPs in Q1–3, 2017 are based on incomplete data and thus very tentative.

TABLE 16.

Conservative estimate of the number of people treated with SOF-based regimens, 2014 to 2016

	Originator European Union, Japan and USA	Originator ROW	Generic	Total
2013	2 000	0	0	**2 000**
2014	174 000	15 000	0	**189 000**
2015	403 000	186 000	157 000	**746 000**
2016	382 000	118 000	736 000	**1 236 000**
Total	**961 000**	**319 000**	**893 000**	**2 173 000**

ROW = Rest of the world.
Source of originator data: Gilead. Re generic estimates, see notes for Figure 21.

According to Gilead, some 1.2 million people worldwide were treated with originator SOF (or a SOF-containing regimen) in the period 2014–2016. Over 75% of them were living in high-income countries; the others were living mainly in Brazil, Egypt or Pakistan [*203–205*].

Meanwhile, based on domestic consumption and export data from India, it is estimated that worldwide at least 887 000 people accessed generic SOF or SOF-based treatments in 2015 and 2016. This number does not include the use of generics produced with non-Indian SOF API.

According to these estimates, in 2016, the number of people treated with generics worldwide surpassed the number treated with originator medicines; since the last quarter of 2016, the number of people able to access generic DAAs has been significantly larger than the number of people with access to originator medicines.

These numbers show that the market for, and access to, generic SOF-containing regimens is developing much more rapidly than was the case for ARVs – even though the estimated global HCV market is significantly smaller than that for first-line ARVs (71 million people requiring 12 weeks of treatment for HCV versus 36 million people on lifelong treatment with ARVs)[20].

At the same time, these estimates indicate that in 2015 the total number of people treated with SOF-based DAAs is less than the estimated number of new cases (1.75 million [10]). Even in 2016, the number of people accessing SOF-based DAA treatment is likely to have been lower than the number of new HCV infections[21].

[20] In metric tons, the total amount of SOF required to cure 71 million cases of chronic HCV infection is about 1.5 times the yearly requirement for tenofovir (a key first-line ARV).
[21] As mentioned, the estimates for people able to access DAA treatment are low-end estimates.

Market forces

In the first part of 2015, the price of DAAs was the single largest factor limiting demand and uptake. With the rapid decrease in generic prices, the cost of treatment is less of a hurdle today – though price still is a key barrier to access in countries where patents prevent the use of generics.

Following a brief review of the level of market penetration of DAAs to date, this section explores the various other factors that affect the development of robust demand for DAAs in low- and middle-income countries.

1. Limited funding for procurement of direct-acting antivirals

Though prices of several key DAAs have fallen sharply over the past year for many low- and middle-income countries, there is still limited funding available to purchase these medicines. Most major international or bilateral donors provide limited or no support for HCV treatment. The Global Fund to Fight AIDS, Tuberculosis and Malaria has opened the door to buying products for HIV/HCV coinfection, subject to conditions.[22]

If DAAs are to be rolled out in low- and middle-income countries, the primary purchasers are likely to be national governments. A number of countries, such as Brazil and Egypt, have set up treatment programmes and are purchasing DAAs. Other countries are preparing to follow suit and are starting to procure HCV medicines (as well as putting the necessary infrastructure in place). Nevertheless, in most low- and middle-income countries there is currently little or no funding for HCV treatment.

The private sector can also play a role in the financing and provision of DAAs; in some countries, such as Pakistan, this role is significant [*153*].

However, overall, generic procurement volumes are relatively low, and there is little sustainable financing. This results in an uncertain market for generic suppliers of DAAs.

2. Patient initiatives

Decisions by some governments or insurers to provide DAAs only to patients with advanced liver disease, or not to provide HCV treatment at all, leaves many people who are diagnosed with HCV infection without access to a cure. Knowing that cures exist, some take matters into their own hands.

[22] Decision Point GF/B33/DP08. Policy on coinfections and comorbidities. Geneva: The Global Fund; April 2015.

In a number of countries, including for example Australia and the United Kingdom, individual patients have the legal right to import medicines for their personal use. People from these countries reportedly have travelled to Egypt or India to seek treatment there or to buy more affordable (generic) DAAs. [23]

A related phenomenon is the emergence of "buyers' clubs" – organizations that advise on and facilitate the purchase and importation of generic DAAs by individual patients through the Internet.[24] Obtaining medicines through Internet orders from suppliers in other countries is obviously not ideal and entails the risk of receiving substandard products unless ways can be found to assure the quality of the generic product and the integrity of the supply chain. Despite uncertainty about the quality, treatment outcomes reportedly achieved by people accessing DAAs through buyers' clubs are similar to those achieved in regular clinical practice (see Annex 14). Moreover, as long as relatively large numbers of people who are diagnosed with HCV cannot access treatment through the domestic health care system in their country, there will continue to be a market for buyers' clubs or similar approaches.

3. Demand impediments: lack of testing and low awareness

Where prices of medicines have fallen significantly, uptake of DAAs is limited by the fact that the majority of people with HCV do not know they are infected; globally, it is estimated that only Some 20% of people with chronic hepatitis have been diagnosed [*10*].[25] The diagnostic algorithm, while undergoing simplification, is still relatively complex[26] – and expensive. Partners and implementers working in different low- and middle-income countries report that the cost of testing and diagnosis may now exceed the cost of treatment.[27] Facilities for screening and diagnosis are still limited in many countries.

The low level of awareness about HCV means furthermore that, in most countries, few people seek to be tested for HCV.

Once patients who have been diagnosed in the past, but were waiting for the DAAs to become available, or affordable (rather than undergoing the difficult treatment with Peg-IFN) have received treatment, volumes may go down; this trend is already seen in several high-income countries (see Figure 21). At that stage, offering HCV screening, diagnosis and treatment to high-risk groups that can be reached – such as people living with HIV

[23] For example, an organization in Egypt offers testing and treatment for HCV to foreigners, combined with tourism (http://tourncure.com/).
[24] Some of the more established buyers' clubs include FixHepC and Hepatitis C Treatment Without Borders. Both are based in Australia and have been in operation since 2015. They help arrange shipments of generic DAAs to a wide range of countries. There are also buyers' clubs in China, the Russian Federation and South-East Asia
[25] According to WHO, this number is much lower in the African Region (6%) and in the South-East Asia Region (9%) [*10*].
[26] The availability of pan-genotypic regimens contributes to simplification of the diagnostic algorithm.
[27] This was, for instance, reported during the HCV intervenors meeting in Geneva on 20 March 2017, organized by Coalition Plus.

who are receiving HIV treatment, injecting drug users attending harm reduction programmes or on opioid substitution therapy, prisoners, or children born to HCV-positive mothers – represents an important way forward. It would facilitate the finding of HCV-positive patients and may contribute significantly to efforts to reduce new infections (as some of these groups are driving the HCV epidemic). For instance, the Indian State of Punjab, which has been very proactive in setting up a free HCV treatment programme, is already considering this approach [*209–211*].

4. Other impediments to uptake

Several other factors have the potential to impede or slow down the uptake of DAAs.

- *Lack of prioritization and national strategies*. The prevention, diagnosis and treatment of hepatitis C are often not included in national health plans. The lack of prioritization and resources delays the implementation of many measures that are prerequisite steps for expanding access. The adoption of the global health sector strategy on viral hepatitis has, however, helped to put viral hepatitis on the agenda of ministries of health.

- *Regulatory delays*. Delays in national registration of key DAAs have the potential to delay the availability of these drugs to patients who urgently need them. This risk is especially pronounced in countries with weak regulatory authorities, in countries that mandate in-country clinical trials as a prerequisite for approval, and in countries where registration is not prioritized by manufacturers.

- *Lack of up-to-date treatment guidelines*. The standard of care for HCV treatment is rapidly evolving. Normative bodies at global and national levels may struggle to keep pace with the latest scientific and medical evidence, potentially delaying the introduction of optimal regimens.

- *Insufficient human resources and health systems*. Health-care personnel will need to be trained to diagnose HCV and administer novel HCV treatments, and the supply chain will need to be strengthened. Even when integrating HCV treatment into existing programmes such as those for HIV, some additional infrastructure will be required.

- *Stigma and discrimination*. Some national governments may refrain from prioritizing HCV treatment because of the epidemic's (perceived) concentration in marginalized and stigmatized populations, such as people who inject drugs.[28] This phenomenon has already been observed during the HIV epidemic, as national governments have largely failed to allocate substantial domestic resources to treatment and prevention programmes for these key populations [*9*]. While 37% of all adults living with HIV globally received ART in 2013, UNAIDS estimates that only 10% of people who inject drugs accessed HIV treatment [*9*]. To the extent that HIV treatment and prevention programmes have been implemented for key populations in low- and middle-income countries, this has typically happened as a result of support from external donors. In the case of HCV treatment, however, no comparable donor initiative has yet emerged.

[28] WHO estimates that 8% of people with chronic HCV infection are injecting drug users [*10*]. Injecting drug users and other key populations may be more likely to know they are infected with HCV (compared to the general population).

Annexes

Annex 1. Overview of single ingredient products

This annex summarizes key data on products that contain a single DAA and which are currently on the market. Additional information on recommended products can be found in Annex 2.

Asunaprevir

Asunaprevir is a twice-daily HCV protease inhibitor. It was approved in Japan, for use in combination with daclatasvir, in 2014.[29] In October 2014, however, Bristol-Myers Squibb withdrew its USFDA application for this combination, citing the rapid evolution of HCV treatments. Asunaprevir can be hepatotoxic and requires frequent liver enzyme monitoring.

Boceprevir and telaprevir

The protease inhibitors boceprevir and telaprevir were approved in 2011 for use with Peg-IFN and RBV as response-guided therapy. The complexity, toxicity, twice-daily or three times daily dosing, and the availability of newer, oral, interferon-free regimens has made them obsolete; they are no longer recommended by AASLD/IDSA, EASL or WHO [*5, 67, 68*]. Telaprevir was withdrawn from the United States market in 2014 [*212*], followed by boceprevir in 2015 [*213*]. Both medicines continue to be sold in many other countries.

Daclatasvir

DCV is the first NS5A inhibitor. It received regulatory approval in the European Union and Japan in 2014. DCV is safe and well tolerated. Dosing is once a day, and there are no special food requirements. DCV is the only approved "stand-alone" NS5A inhibitor; the other approved NS5A inhibitors are available only in an FDC.

Dasabuvir

Dasabuvir is a non-nucleoside polymerase inhibitor that received initial regulatory approval in late 2014 for use in combination with ombitasvir/paritraprevir/ritonavir. The addition of dasabuvir increases the cure rate of this combination regimen in genotype 1. Patients with genotype 1a and some patients with genotype 1b must take RBV with this regimen.

[29] The mix of genotypes in Japan is unique: genotype 1b is the dominant genotype (followed by genotype 2), while genotype 1a is very rare.

Simeprevir

SIM, the first once-daily HCV protease inhibitor, was approved in Canada, Japan and the USA in 2013. Although originally developed to be used in genotypes 1 and 4 in combination with Peg-IFN + RBV, in October 2014 the USFDA approved the IFN-free, RBV-free, 12–24-week combination of SIM + SOF for the treatment of genotype 1.

SIM has also been studied with daclatasvir [*214, 215*]. It is currently being studied with AL-335 (a nucleoside polymerase inhibitor) and odalasvir (a protease inhibitor), see below.

SIM has some inherent limitations. It does not have pan-genotypic efficacy and cannot be used in combination with many antiretroviral medicines, including HIV protease inhibitors, cobicistat-based regimens, and most non-nucleoside reverse transcriptase inhibitors. SIM is not recommended for people with advanced cirrhosis. Because it can cause rash and photosensitivity, patients receiving SIM are advised to avoid direct exposure to the sun, and to use sunblock, hats and protective clothing during treatment. While the development of SIM represented a step forward in the evolution of HCV treatments, its role in low- and middle-income countries will probably be limited.

Sofosbuvir

SOF is a once-daily, pan-genotypic nucleoside polymerase inhibitor; it is the backbone of most HCV treatment regimens currently on the market. SOF is potent, has a high genetic barrier to the development of resistance, is associated with few drug–drug interactions, and is safe and well tolerated. SOF must be used in combination with other anti-HCV medicines. Current WHO treatment guidelines recommend the use of SOF with daclatasvir, ledipasvir, SIM and/or RBV depending on the genotype [*5*] (see Table 4 in Chapter 4).

SOF and SOF-based combinations have been studied in treatment-naïve and treatment-experienced patients, in persons with HCV mono-infection and HIV/HCV coinfection, and in patients with and without cirrhosis. Typically, cure rates are above 95%, except in persons with genotype 3 and cirrhosis. There are limited data on SOF-based combinations in genotypes 5 and 6.

Vaniprevir

In September 2014, vaniprevir, an oral twice-daily protease inhibitor was approved in Japan. Merck has announced that it plans to make vaniprevir available only in Japan.[30]

[30] The mix of genotypes in Japan is unique: genotype 1b is the dominant genotype (followed by genotype 2), while genotype 1a is very rare.

Annex 2. Overview of key direct-acting antivirals/regimens

This annex summarizes additional information on DAAs/regimens that are currently on the market and that are recommended by AASLD/ISDA, EASL and/or WHO.

DAA/Regimen Class(es) Originator	Pan–genotypic	Comments and cautions
simeprevir (Olysio®) NS3/4A protease inhibitor; 150 mg QD; Janssen	No	• Effective for HCV genotypes 1 and 4 • Must be used with other DAAs • Longer treatment recommended for cirrhosis • Has been used with and without RBV • Can cause photosensitivity; sun protection is recommended during use • Drug interactions limit HIV treatment options • Not recommended for persons with Child-Pugh Class C cirrhosis
sofosbuvir (Sovaldi®) NS5B nucleotide polymerase inhibitor; 400 mg QD; Gilead Sciences	YES	• Must be used with other DAAs • Backbone of most regimens • Has been used with and without RBV • Duration of treatment varies • High barrier to resistance • Can be used with ARVs (except tipranavir) • Contraindicated with amiodarone (co-administration can cause heart failure) • Drug interactions with antimycobacterials • No dose recommendation for severe renal impairment/end-stage renal disease • Paediatric trial (with RBV) underway
daclatasvir (Daklinza®) NS5A inhibitor; 60 mg QD; Bristol-Myers Squibb	Likely	• Must be used with other DAAs • Has been used with and without RBV • Longer treatment and/or addition of RBV recommended for cirrhosis • Less effective in genotype 3/cirrhosis • Limited data in genotypes 5 and 6 • Safe in advanced liver and kidney disease, pre- and post-transplant • Can be used with most ARVs; dose adjustment needed with efavirenz and boosted atazanavir • Drug interactions with antimycobacterials

DAA/Regimen Class(es) Originator	Pan–genotypic	Comments and cautions
Harvoni® FDC: sofosbuvir + ledipasvir NS5B nucleotide polymerase inhibitor + NS5A inhibitor; 400 + 90 mg QD; Gilead Sciences	No	• Effective against genotypes 1, 4, 5 and 6 • Not recommended for genotypes 2 or 3 • Used with and without RBV • Treatment duration varies according to HCV treatment history, stage of liver disease and baseline HCV RNA • Can be used with most ARVs • Kidney function monitoring recommended when used with TDF, especially for regimens that include a boosted HIV protease inhibitor • Contraindicated with amiodarone (co-administration can cause heart failure) • No dose recommendation for severe renal impairment/end-stage renal disease • Drug interactions with antimycobacterials, antacids, H2-receptor antagonists and proton pump inhibitors • Paediatric trials underway
Viekirax® + Exviera®/ Viekira Pak® FDC (2 tablets): paritaprevir/r/ ombitasvir; + dasabuvir ± RBV; ritonavir-boosted NS3/4a protease inhibitor + NS5A inhibitor; NS5B non-nucleoside polymerase inhibitor; 75 + 50 + 12.5 mg/QD; 250 mg/BD; AbbVie	No	• Effective against genotype 1; Viekirax® + RBV used for genotype 4 • RBV is required for genotype 1a • Longer treatment recommended for genotype 1a/ cirrhosis • Vigilant monitoring recommended in advanced cirrhosis (Child Pugh Class B or Class C) – especially during the first 4 weeks of treatment • Drug interactions limit HIV treatment options • Cannot be used with ethinyl estradiol-containing contraceptives • Drug interactions with antimycobacterials
Zepatier® FDC: grazoprevir + elbasvir; protease inhibitor + NS5A inhibitor; 100 + 50 mg/QD; Merck Sharp & Dohme	No	• Approved for genotypes 1 and 4, and used in genotype 3, with sofosbuvir • Also studied in renal impairment, people who inject drugs (on OST), and in genotype 6 • In genotype 1a, baseline resistance testing is recommended • RBV and longer treatment duration recommended for genotype 1a with certain baseline • NS5A resistance-associated variants, and for genotype 4, treatment-experienced • RBV also recommended for genotype 1, treatment-experienced (if past treatment included an HCV protease inhibitor) • Drug interactions limit HIV treatment options • Drug interactions with antimycobacterials
Epclusa® FDC: sofosbuvir + velpatasvir; nucleotide polymerase inhibitor + NS5 inhibitor; 400 + 100 mg/QD; Gilead Sciences	Yes	• 12-week treatment duration regardless of genotype, liver disease stage or HCV treatment history • RBV needed for decompensated cirrhosis • No dose recommendation for severe renal impairment/end-stage renal disease • Contraindicated with amiodarone (co-administration can cause heart failure) • Cannot be used with efavirenz • Kidney function monitoring recommended with TDF • Drug interactions with antimycobacterials, antacids, H2-receptor antagonists and proton pump inhibitors

Source of data: [*88, 95, 99–103, 216, 217*].

Annex 3. Additional data on sofosbuvir + daclatasvir (+/- ribavirin)

This annex summarizes additional information on treatment outcomes of SOF+DCV in genotypes 4–6 and in populations that are difficult to treat (notably those with advanced liver disease).

Source	Population and sample size	Regimen	SVR	Comments
ANRS CULPIT	Post-transplant, HCV genotypes 1, 3, 4 and 5, treatment-naïve or treatment-experienced; cirrhotic and non-cirrhotic N = 137	SOF+DCV ± RBV, for 12 or 24 weeks	SOF+DCV, 12 weeks SVR: 100% (21/21)	RBV increased AEs; dose reduction was used in 35%, and 15% discontinued treatment for this reason. Small but significant reduction in renal function reported during treatment.
			SOF+DCV + RBV, 12 weeks SVR: 75% (3/4)	
			SOF+DCV, 24 weeks SVR: 97% (66/68)	
			SOF+DCV + RBV, 24 weeks SVR: 95% (42/44)	
ANRS HEPATER	HCV genotype 1, N = 768	SOF+DCV ± RBV, for 12 or 24 weeks	SOF+DCV, 12 weeks SVR: 92% (147/160)	Cure rates slightly lower in people with cirrhosis (overall 94% [528/563] versus 98% [201/205]). Highest cure rates seen with 12 weeks of SOF+DCV (no cirrhosis) or 24 weeks (cirrhosis). RBV increased treatment discontinuation for AEs.
			SOF+DCV + RBV, 12 weeks SVR: 94% (32/34)	
			SOF+DCV, 24 weeks SVR: 95% (417/439)	
			SOF+DCV + RBV, 24 weeks SVR: 99% (133/135)	
			SOF+DCV + RBV, 12 weeks SVR: 75% (3/4)	
			SOF+DCV, 24 weeks SVR: 97% (66/68)	
			SOF+DCV + RBV, 24 weeks SVR: 95% (42/44)	

Source	Population and sample size	Regimen	SVR	Comments
European Compassionate Use Programme	HCV genotypes 1, 2, 3, 4, 5; People with urgent need for treatment: high risk for liver failure/death; post-transplant; or extrahepatic manifestations, comorbidities, including HIV/HCV N = 485	SOF+DCV ± RBV, for 24 weeks	SOF+DCV SVR: 92% (313/341)	Group included people with decompensated cirrhosis. None of 10 deaths that occurred during the study were treatment-related.
			SOF+DCV + RBV SVR: 89% (106/119)	
French Daclatasvir ATU Programme	HCV genotypes 4, 5, 6 People with pre-cirrhosis or cirrhosis, including HIV/HCV N = 246	SOF+DCV ± RBV, for 12 or 24 weeks	SOF+DCV, 12 weeks Genotype 4 SVR: 84% (53/63) Genotype 5 SVR: 100% (10/10) Genotype 6 SVR: 100% (4/4)	7 deaths occurred during this study; none were considered treatment-related.
			SOF+DCV + RBV, 12 weeks Genotype 4 SVR: 88% (7/8) Genotype 5 SVR: n/a Genotype 6 SVR: n/a	
			SOF+DCV, 24 weeks Genotype 4 SVR: 93% (102/110) Genotype 5 SVR: 100% (14/14) Genotype 6 SVR: 100% (1/1)	
			SOF+DCV + RBV, 24 weeks Genotype 4 SVR: 97% (30/31) Genotype 5 SVR: n/a Genotype 6 SVR: 100% (1/1)	

Note: AEs = adverse events.
Source of data: [*217–221*].

Annex 4. Performance versus target product profile

The table below summarizes the characteristics and treatment outcomes of the two pan-genotypic regimens currently on the market (SOF + DCV and SOF/VEL) versus the target product profile.

SVR >90%	Pan-genotypic	Safe, tolerable	QD	Treatment duration	RBV needed	Data in HIV/HCV; DDIs with ARVs	Comments
SOF+DCV							
Yes, except in genotype 3 + cirrhosis, especially if treatment-experienced (SVR 88% or 14/16 after 12 weeks of SOF+DCV +RBV)	Small numbers of genotypes 5 and 6	Yes	Yes	12, 18 or 24 weeks	For cirrhosis	Yes; SVR comparable to HCV mono-infection; DDIs can be managed with DCV dose adjustment	More data needed on genotypes 5 and 6 and for optimizing treatment duration and outcomes; has been used safely and effectively in thousands of people via compassionate use, cohort studies and in real-life settings
SOF/VEL							
Yes, except in treatment-experienced with genotype 3/ cirrhosis, (SVR 89% or 33/37 after 12 weeks of SOF/VEL)	Yes, limited data on genotypes 5 and 6	Yes	Yes	12 weeks	For decompensated cirrhosis	Yes; SVR comparable to HCV mono-infection. Cannot be used with efavirenz	Data only in selected population from clinical trials; real-life data needed

Source of data: [*103, 218–220,222–228*].

Annex 5. Use of direct-acting antivirals with contraceptives or during pregnancy

The table below summarizes the recommendations on use during pregnancy and indicates whether the product can be used with hormonal contraction. The information is based on the package inserts approved by the EMA and the USFDA (as of January 2017), and on an article in the New England Journal of Medicine [*229*].

Product	EMA	USFDA	Can be used with hormonal contraception?
Daclatasvir (NS5A inhibitor); Daklinza®	No human data; in animals, daclatasvir is embryotoxic and teratogenic in rats and rabbits at exposures at or above 4-fold (rat) and 16-fold (rabbit) the clinical AUC exposure. Daklinza® should not be used during pregnancy or in women of childbearing potential not using contraception. Use of highly effective contraception should be continued for 5 weeks after completion of Daklinza® therapy.	No human data available; in animals, no fetal harm at exposures 6 (rats) and 22 (rabbits) times higher than the recommended human dose; no developmental toxicity with maternal systemic exposure (AUC) approximately 3.6 times higher than the recommended human dose . At much higher doses, maternal and fetal toxicity occurred.	Yes; ethinylestradiol 35 µg and norgestimate 0.180/0.215/0.250 mg is recommended.

Product	EMA	USFDA	Can be used with hormonal contraception?
Grazoprevir/elbasvir (protease inhibitor/ NS5A inhibitor); Zepatier®	There are no adequate and well-controlled studies with Zepatier® in pregnant women. Animal studies do not indicate harmful effects with respect to reproductive toxicity. Because reproduction animal studies are not always predictive of human response, Zepatier® should be used only if the potential benefit justifies the potential risk to the fetus.	No adequate human data are available to establish whether or not Zepatier® poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of Zepatier® (elbasvir or grazoprevir) at exposures greater than those in humans at the recommended human dose.	Yes
Simeprevir (HCV protease inhibitor); Olysio®	There are no adequate and well-controlled studies with simeprevir in pregnant women. Studies in animals have shown reproductive effects (see section 5.3). Olysio® should be used only during pregnancy or in women of childbearing potential if the benefit justifies the risk. Female patients of childbearing potential must use an effective form of contraception.	No adequate human data are available. In animal reproduction studies with simeprevir, embryofetal developmental toxicity (including fetal loss) was observed in mice at simeprevir exposures greater than or equal to 1.9 times higher than exposure in humans at the recommended clinical dose, while no adverse embryofetal developmental outcomes were observed in mice and rats at exposures similar to the exposure in humans at the recommended clinical dose. Given these findings, pregnant women should be advised of potential risk to the fetus.	Yes
Paritparevir/r/ ombitasvir+ dasabuvir (boosted HCV protease inhibitor/ NS5A inhibitor + non-nucleoside polymerase inhibitor); Viekira Pak®, Vikerax®, Exviera®	There are very limited data from the use of Viekirax® in pregnant women. Studies with ombitasvir and paritaprevir/ritonavir in animals have shown malformations. The potential risk for humans is unknown. Viekirax® should not be used during pregnancy or in women of childbearing potential not using effective contraception.	No or limited human data; in animals, no fetal harm at higher exposures than the recommended human dose. Viekira Pak® should be used during pregnancy only if clearly needed.	No; ethinyl estradiol is contraindicated.
Ribavirin	**CONTRAINDICATED; women and their male partners should avoid pregnancy for 6 months after treatment with ribavirin**		Yes

Product	EMA	USFDA	Can be used with hormonal contraception?
Sofosbuvir (nucleotide polymerase inhibitor); Sovaldi®	No or limited human data. As a precautionary measure, it is preferable to avoid the use of sofosbuvir during pregnancy.	Animal reproduction studies have failed to demonstrate a risk to the fetus. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of the human response, Sovaldi® should be used during pregnancy only if the potential for benefit justifies the potential risk to the fetus.	Yes
Sofosbuvir/ ledipasvir (nucleotide polymerase inhibitor/NS5A inhibitor); Harvoni®	As a precautionary measure, it is preferable to avoid the use of Harvoni® during pregnancy.	No human data; in animals, no fetal harm at higher exposures than the recommended human dose.	Yes
Sofosbuvir/ velpatasvir (nucleotide polymerase inhibitor/NS5A inhibitor); Epclusa®	As a precautionary measure, Epclusa® use is not recommended during pregnancy.	No human data; in animals, no fetal harm at higher exposures than the recommended human dose.	Yes

Annex 6. Retreatment trials and results

The table below provides an overview of information and outcomes of retreatment trials.

Study and population	Regimen	Results	Comments
Esteban R et al. genotype 3, SOF-experienced, 40% cirrhotic N = 38	24 weeks of SOF + RBV	SVR: 63% (24/38)	Interim analysis; no final SVR data. SVR lower in cirrhotic participants than in non-cirrhotic: 47% (7/15) versus 74% (17/23).
Gane EJ et al. genotype 1, SOF-experienced, N = 19	12 weeks of SOF/LDV + RBV	SVR: 100% (19/19)	
Lawitz E et al. genotype 1, prior – 8 or 12 weeks SOF/LDV, ± RBV or GS-9669, 46% cirrhosis N = 41	24 weeks of SOF/LDV	SVR: 71% (29/41)	People who were previously treated for 8 weeks were more likely to be cured than people who were treated for 12 weeks: 80% (24/30) versus 46% (5/11).
Nelson DR et al. ALLY-3 trial genotype 3, SOF-experienced, 27% cirrhosis N = 7	12 weeks of SOF + DCV	SVR: 71% (5/7)	
Osinusi A et al. genotype 1, SOF-experienced N = 14	12 weeks of SOF/LDV	SVR: 100% (14/14)	
Wyles D et al. genotype 1, SOF-experienced N = 45	12 weeks of SOF/LDV + RBV	SVR: 98% (44/45)	The one person who was not cured had genotype 3a.
Ledinghen V et al. genotypes 1 or 4, prior – SOF +/- RBV with SIM, DAC or LDV N = 26	16 weeks of SOF/GZR/ELB/RBV	SVR4: 100% (13/13)	Pilot study – ongoing.
	24 weeks of SOF/GZR/ELB/RBV	SVR4: 91% 10/11	1 death – unrelated to study medicine.

Study and population	Regimen	Results	Comments
Ouzan D et al. genotypes 1a, 2, 3, 4 prior - SOF with PEG+RBV or LDV or RBV, N = 10	24 weeks of SOF+DCV +/- RBV	SVR: 90% (9/10)	1 ongoing.
Ouzan D et al. genotypes 1a and 1b prior - SOF with PEG+RBV or RBV, N = 3	12/24 weeks of SOF/LED +/- RBV	SVR: 100% (3/3)	
Ouzan D et al. genotypes 1a & 1b prior - SOF with PEG+RBV or LDV N = 2	12/24 weeks of SOF/SIM +/- RBV	SVR: 50% (1/2)	RAS at HS5A site for patient with previous LDV treatment - subsequent relapse following SOF/SIM+RBV.
Ouzan D et al. genotype 4 prior - SOF with PEG+RBV N = 1	12 weeks with Viekirax®	SVR: 100% (1/1)	
Ouzan D et al. genotype 1 prior - SOF with LDV N = 1	16 weeks with SOF+GZR+ELB+RBV	SVR: 100% (1/1)	RAS at NS5A site – achieved SVR with second treatment.
Ouzan D et al. genotype 2 prior - SOF with RBV N = 1	12 weeks with SOF+PEG+RBV	SVR: 100% (1/1)	
Cento V et al. genotypes 1, 1a, 1b and 4d (Total patients: 121) prior - boceprevir (51), telaprevir (69) &SIM (1) N = 60	12 or 24 weeks with SOF/LDV+RBV	SVR: 95% (57/60)	3 patients with virological failure that were part of the EASL/AASLD recommended group (non-genotypic resistance-testing [GRT] group).
Cento V et al. As above N = 18	12 or 24 weeks with SOF+DCV +/-RBV	SVR: 94% (17/18)	1 patient with virological failure as part of the EASL/AASLD recommended group (non-genotypic resistance-testing [GRT] group).
Cento V et al. As above N = 7	12 or 24 weeks with 3D (paritaprevir/ritonavir/ ombitasvir and dasabuvir) + RBV	SVR: 100% (7/7)	
Cento V et al. As above N = 30	12 or 24 weeks with SOF+SIM+/-RBV	SVR: 87% (26/30)	4 patients with virological failures as part of the non-EASL/AASLD recommended and non-GRT guided group.

Study and population	Regimen	Results	Comments
Ouzan D et al. genotypes 1a, 2, 3, 4 prior - SOF with PEG+RBV or LDV or RBV, N = 10	24 weeks of SOF+DCV +/- RBV	SVR: 90% (9/10)	1 ongoing.
Hezode C et al. genotype 1a prior - either DCV/PR or DCV/ASV/PR, Total patients 15, cirrhosis 56% N = 10	12 weeks with SIM/SOF	SVR: 80% (8/10)	Treatment failures: Patient 1: female, cirrhotic, prior treatment with DCV/PR. Patient 2: male, cirrhotic, prior treatment DCV/ASV/PR.
Hezode C et al. genotype 1b prior - as above N = 3	12 weeks with SIM/SOF	SVR:100% (3/3)	
Hezode C et al. genotype 4 prior - as above N = 2	12 weeks with SIM/SOF	SVR:100% (2/2)	
Poordad et al. 2016 genotype 1 prior - NS3 PI and/or NS5A inhibitor +/- SOF	12 weeks with GLE 200mg + PIB 80mg	SVR: 100% (6/6)	
As above	12 weeks with GLE 300mg + PIB 120mg + RBV 800mg	SVR: 95% (21/22)	1 patient relapsed.
As above	12 weeks with GLE 300mg + PIB 120mg	SVR: 86% (19/22)	2 patients lost to follow-up (achieved SVR). 1 patient had virological breakthrough.
Wilson et al. 2015 genotype 1 prior - SOF/LDV short course	12 weeks with LDV/SOF	SVR: 91% (31/34)	1 patient relapsed. 2 patients lost to follow-up.
Bourliere et al. 2015 genotype 1 prior - PI therapy	12 weeks with LDV/SOF	SVR: 97% (75/77)	2 patients relapsed.
Kwo et al. 2015 (C-EDGE –TE) genotype 1 prior- PR	12 or 16 weeks with GZR/ELB +/- RBV	SVR: 95% (357/376)	Virological failure and safety not assigned by genotype.
As above genotype 4	12 or 16 weeks with GZR/ELB +/- RBV	SVR: 86% (32/37)	Virological failure and safety not assigned by genotype.
As above genotype 6	16 weeks with GZR/ELB +/- RBV	SVR: 83% (5/6)	Virological failure and safety not assigned by genotype.

Notes: ELB = elbasvir; GLE = glecaprevir; GZR = grazoprevir; PIB = pibrentasvir.
Source : [*230–235*].

Annex 7. List of direct-acting antivirals (Phase II and beyond)

Phase [31]	Class	INN	Code	Company
Launched	NS3/4A inhibitor	boceprevir		Merck
Launched	NS3/4A inhibitor	telaprevir		Vertex
Launched	NS3/4A inhibitor	simeprevir	TMC-435	Janssen
Launched	Nucleoside NS5B inhibitor	sofosbuvir	GS-7977	Gilead
Launched	NS5A inhibitor	daclatasvir	BMS-790052	Bristol-Myers Squibb
Launched	NS5A inhibitor	ledipasvir	GS-5885	Gilead
Launched	Non-nucleoside NS5B inhibitor	dasabuvir	ABT-333	AbbVie
Launched	NS5A inhibitor	ombitasvir	ABT-267	AbbVie
Launched	NS3/4A inhibitor	paritaprevir	ABT-450	AbbVie
Launched	NS3/4A inhibitor	asunaprevir	BMS-650032	Bristol-Myers Squibb
Launched	NS3/4A inhibitor	vaniprevir	MK-7009	Merck
Launched	NS5A inhibitor	elbasvir	MK-8742	Merck
Launched	NS3/4A inhibitor	grazoprevir	MK-5172	Merck
Launched	NS5A inhibitor	velpatasvir	GS-5816	Gilead
III	NS3/4A inhibitor	danoprevir*	RG-7227	Roche
III	NS3/4A inhibitor	glecaprvir	ABT-493	AbbVie
III	NS5A inhibitor	pibrentasvir	ABT-530	AbbVie
III	NS3/4A inhibitor	voxilaprevir	GS-9857	Gilead
II/III	NS5A inhibitor	ravidasvir	PPI-668	Presidio Pharma

[31] Launched means the product has been launched in at least one country.

Phase [31]	Class	INN	Code	Company
II	NS5A inhibitor	odalasvir	ACH-3102	Achillion
II	NS5A inhibitor	ruzasvir	MK-8408	Merck
II (?)	NS3/4A inhibitor	sovaprevir	ACH-1625	Achillion
II	Nucleoside NS5B inhibitor		AL-335	Alios BioPharma
II	Nucleotide NS5B inhibitor	uprifosbuvir	MK-3682	Merck

* Being developed in Asia only. (?) = uncertain if development is still ongoing.

Annex 8. Hepatitis C virus regimens in the pipeline

The table below provides an overview of HCV regimens in the development pipeline (phases II and III).

Status	Regimen, duration, SVR	Comments
MK-3682 + grazoprevir + ruzasvir (nucleotide polymerase inhibitor, 225mg/QD; HCV protease inhibitor, 50mg/QD; NS5A inhibitor, 30mg/QD) *Sponsor*: Merck Sharp & Dohme		
Phase II; multiple studies underway	Genotype 1a, treatment-naïve; 8 weeks SVR: 93% (39/42)	Under study in HCV genotypes 1, 2 and 3, compensated cirrhosis, HIV/HCV coinfection, treatment-naïve and DAA-experienced people. 12 weeks more effective than 8 weeks. Weakness of this regimen seen in genotype 3, especially with shorter treatment or baseline NS5A resistance (Y93H); RBV did not improve SVR rates.
	Genotype 1a, treatment-naïve; 12 weeks SVR: 98% (47/48)	
	Genotype 1b treatment-naïve; 8 weeks SVR: 98% (45/46)	
	Genotype 1b, treatment-naïve 12 weeks SVR: 100% (40/40)	
	Genotype 2, treatment-naïve; 8 weeks ± RBV SVR: 86% (54/63)	
	Genotype 2, treatment-naïve; 12 weeks ± RBV SVR: 97% (60/62)	
	Genotype 2, treatment-naïve; 16 weeks SVR: 100% (26/26)	
	Genotype 3, treatment-naïve or treatment-experienced; 8 weeks ± RBV SVR: 95% (98/103)	
	Genotype 3, treatment-naïve or treatment-experienced; 12 weeks ± RBV SVR: 97% (155/159)	
	Genotype 3, treatment-naïve or treatment-experienced, 16 weeks ± RBV SVR: 96% (72/75)	

Status	Regimen, duration, SVR	Comments
AL-335 + odalasvir ± SIM (nucleotide polymerase analog, 800 mg QD; NS5A inhibitor, 25mg QD; protease inhibitor, 75mg/QD). *Sponsors*: Alios BioPharma/Achillion/Janssen		
Phase II (AL-335 and odaslavir; SIM is approved)	2 medicines; 8 weeks SVR: 90% (18/20)	Genotypes 1 and 3, treatment-naïve, includes compensated cirrhosis. Results not specified by genotype or cirrhosis. SIM was approved for use in genotypes 1 and 4 only. Moving into phase IIb for HCV genotypes 1, 2, 4, 5 and 6; under study in genotypes 2 and 3, in treatment-naïve or treatment-experienced people with or without compensated cirrhosis. Cardiac abnormality led to treatment discontinuation, probably related to odalasvir and possibly to AL-335 and SIM.
	3 medicines; 6 weeks SVR: 100% (20/20)	
	3 medicines; 8 weeks SVR: 100% (40/40)	
Ravidasvir/sofosbuvir (NS5A inhibitor, 200mg/QD; nucleotide polymerase inhibitor 400 mg/QD) *Sponsor*: Drugs for Neglected Diseases Initiative (DNDi)		
Phase II/III opened in 2016 in Malaysia and Thailand	No cirrhosis, treatment-naïve; 2 drugs, 12 weeks SVR: 100% (45/45)	SVR data currently are available only for genotype 4. Ongoing trial, based on simplicity; for non- cirrhotic people, 12 weeks of treatment; for people with cirrhosis, 24 weeks of treatment.
	No cirrhosis, treatment-naïve 12 weeks + RBV SVR: 98% (44/45)	
	No cirrhosis, treatment-experienced; 2 drugs, 12 weeks SVR: 95% (38/40)	
	No cirrhosis, treatment-experienced 12 weeks + RBV SVR: 100% (40/40)	
	Cirrhosis, treatment-naïve; 2 drugs, 12 weeks SVR=93% (29/31)	
	Cirrhosis, treatment-naïve; 12 weeks + RBV SVR: 92% (37/40)	
	Cirrhosis, treatment-experienced; 12 weeks + RBV SVR: 86% (27/31)	
	Cirrhosis, treatment-experienced; 16 weeks + RBV SVR: 100% (40/40)	

Status	Regimen, duration, SVR	Comments
Glecaprevir/pibrentasvir ± RBV (protease inhibitor, 300 mg/QD0; NS5A inhibitor, 120mg/QD). Sponsor: AbbVie		
Phase III (submitted to FDA on 19 December 2016; approval anticipated in second quarter 2017)	Genotype 1, treatment-naïve or treatment-experienced, with or without compensated cirrhosis, includes HIV+; 8 weeks SVR: 99% (348/351) 12 weeks SVR: 99.7% (351/352)	In phase III, no trial in genotype 3 with compensated cirrhosis. Trial in compensated cirrhosis in genotypes 2, 4, 5 and 6 underway. Safe and effective in renal impairment, with or without compensated cirrhosis; SVR: 98% (102/104). Well tolerated, safe, highly effective. Dolutegravir-, raltegravir- or rilpivirine-based regimens: drug interactions may limit HIV treatment options with this regimen.
	Genotype 2, treatment-naïve or treatment–experienced, no cirrhosis; 12 weeks SVR: 99% (195/196)	
	Genotype 4, treatment-naïve or treatment-experienced, no cirrhosis 12 weeks SVR: GT4: 99% (75/76)	
	Genotype 5, treatment-naïve or treatment-experienced, no cirrhosis; 12 weeks SVR: 100% (26/26)	
	Genotype 6, treatment-naïve or treatment-experienced, no cirrhosis; 12 weeks SVR: 100% (19/19)	
Sofosbuvir/velpatasvir/voxilaprevir (Nucleotide polymerase inhibitor 400 mg/QD; NS5A inhibitor 100 mg/QD; protease inhibitor 100 mg/QD) Sponsor: Gilead Sciences		
Phase III (Submitted to USFDA on 8 December 2016; approval anticipated in second quarter 2017)	POLARIS-1 NS5A-experienced, all genotypes, 46% with cirrhosis (N = 415); 12 weeks SOF/VEL (versus placebo) SVR: 96% (253/263)	SOF/VEL/VOX is safe and effective for 8 weeks in treatment-naïve (except for genotype 1a, where 12 weeks may be more effective) and as a retreatment regimen, for 8 or 12 weeks. Of note, in POLARIS-2, the relapse rate among treatment-naïve people was higher with SOF/VEL/VOX than SOF/VEL (21 versus 3, most in genotype 1a), but in POLARIS-4, the relapse rate among treatment-experienced people was higher with SOF/VEL (14 versus 1). Both SOF/VEL and SOF/VEL/VOX performed well in genotype 3/cirrhosis. SOF/VEL/VOX was more effective in cirrhosis and persons with multi-class resistance and in genotype 1a (SVR 98% versus 89%) and genotype 3 (94% versus. 85%). Most common side-effects were headache, diarrhoea and nausea. Diarrhoea and nausea more common with SOF/VEL/VOX than with SOF/VEL.
	POLARIS-2 treatment-naïve, all genotypes, 18% cirrhosis (N = 941); 8 weeks SOF/VEL/VOX SVR: 95% (476/501) versus 12 weeks SOF/VEL SVR:98% (432/440)	
	POLARIS-3 treatment-naïve, genotype 3, 100% cirrhosis (N =219); 8 weeks SOF/VEL/VOX versus 12 weeks SOF/VEL; SVR was 96% in both treatment groups	
	POLARIS-4 treatment-experienced (no NS5A experience), genotypes 1, 2, 3, 4, 46% cirrhosis (N = 333); 12 weeks SOF/VEL/VOX SVR: 97% (177/182) versus SOF/VEL SVR: 90% (136/151)	

Source of data: [*78, 79, 104, 137, 138,236–239*]

Annex 9. Originator sales data

TABLE A9-1.

Global originator sales of sofosbuvir (US$ 000s), by quarter-year (Q)

	USA	Europe	Japan	ROW	Total
Q4 2013	136 364	3 071	--	**--**	**139 435**
Q1 2014	2 097 791	163 691	--	13 000	**2 274 349**
Q2 2014	3 031 507	400 218	--	49 000	**3 480 326**
Q3 2014	2 199 519	523 455	--	73 000	**2 796 093**
Q4 2014	1 178 000	459 000	--	95 000	**1 732 000**
Q1 2015	421 000	483 000	--	68 000	**972 000**
Q2 2015	615 000	522 000	62 000	92 000	**1 291 000**
Q3 2015	692 000	337 000	343 000	94 000	**1 466 000**
Q4 2015	660 000	259 000	437 000	155 000	**1 511 000**
Q1 2016	645 000	280 000	202 000	150 000	**1 277 000**
Q2 2016	775 000	263 000	171 000	149 000	**1 358 000**
Q3 2016	363 000	184 000	143 000	135 000	**825 000**
Q4 2016	112 000	164 000	119 000	146 000	**541 000**
Q1 2017	27 000	106 000	N/A	180 000	**313 000**
Q2 2017	61 000	113 000	N/A	141 000	**305 000**
Total	**13 014 181**	**4 250 435**	**1 477 000**	**1 540 000**	**20 281 616**

ROW = Rest of the world. N/A = not available (sales in Japan in 2017 are included in ROW sales data).
Source: Gilead Sciences Inc.

TABLE A9-2.

Global originator sales of SOF/LDV (US$ 000s), by quarter-year (Q)

	USA	Europe	Japan	ROW	Total
Q3 2014	--	19 966a	--	**--**	**19 966**
Q4 2014	2 001 000	83 000	--	23 000	**2 107 000**
Q1 2015	3 016 000	477 000	--	86 000	**3 579 000**
Q2 2015	2 826 000	623 000	--	159 000	**3 608 000**
Q3 2015	2 541 000	532 000	111 000	184 000	**3 332 000**
Q4 2015	1 707 000	587 000	889 000	162 000	**3 345 000**
Q1 2016	1 407 000	555 000	887 000	168 000	**3 017 000**
Q2 2016	1 474 000	512 000	448 000	130 000	**2 564 000**
Q3 2016	1 084 000	380 000	309 000	87 000	**1 860 000**
Q4 2016	976 000	363 000	159 000	106 000	**1 640 000**
Q1 2017	926 000	248 000	N/A	202 000	**1 376 000**
Q2 2017	984 000	230 000	N/A	168 000	**1 382 000**
Total	**18 942 000**	**4 610 000**	**2 803 000**	**1 475 000**	**27 830 000**

ROW = Rest of the world. N/A = not available (sales in Japan in 2017 are included in ROW sales data).
[a] Data refers to "early-access sales" (i.e. before its launch in October 2014) in Europe.
Source: Gilead Sciences Inc.

TABLE A9-3.

Global originator sales of SOF/VEL (US$ 000s), by quarter-year (Q)

	USA	Europe	Japan	ROW	Total
Q2 2016	64 000	--	--	**--**	**64 000**
Q3 2016	593 000	40 000	--	7 000	**640 000**
Q4 2016	934 000	101 000	--	13 000	**1 048 000**
Q1 2017	735 000	138 000	--	19 000	**892 000**
Q2 2017	864 000	248 000	--	59 000	**1 171 000**
Total	**3 190 000**	**527 000**	--	98 000	**3 815 000**

ROW = Rest of the world.
Source: Gilead Sciences Inc.

TABLE A9-4.

Global originator sales of SIM (US$ 000s), by quarter-year (Q)

	USA	ROW	Total
Q4 2013	13 000	10 000	**23 000**
Q1 2014	291 000	63 000	**354 000**
Q2 2014	725 000	109 100	**834 000**
Q3 2014	671 000	133 900	**805 000**
Q4 2014	256 000	78 900	**335 000**
Q1 2015	98 000	140 100	**238 000**
Q2 2015	50 000	215 600	**266 000**
Q3 2015	26 000	53 000	**78 000**
Q4 2015	0[b]	45 000	**45 000**
Q1 2016	16 000	16 000	**32 000**
Q2 2016	21 000	22 000	**43 000**
Q3 2016	13 000	8 000	**21 000**
Q4 2016	5 000	5 000	**10 000**
Total	**2 184 000**	**900 000**	**3 084 000**

ROW = Rest of the world.
[a] Data from Q3 2015 onwards do not include Medivir sales.
[b] Zero due to an accounting adjustment.
Sources: Johnson & Johnson; Medivir. Sales data for the first half of 2017 are not available.

TABLE A9-5.

Global originator sales of asunaprevir and DCV (US$ 000s), by quarter-year (Q)

	asunaprevir			DCV		
	USA	ROW	Total	USA	ROW	Total
Q3 2014	--	11 000	**11 000**	--	38 000	**38 000**
Q4 2014	--	44 000	**44 000**	--	163 000	**163 000**
Q1 2015	--	84 000	**84 000**	--	180 000	**180 000**
Q2 2015	--	97 000	**97 000**	--	382 000a	**382 000a**
Q3 2015	--	72 000	**72 000**	111 000	219 000	**330 000**
Q4 2015	--	35 000	**35 000**	212 000	211 000	**423 000**

Q1 2016	--	7 000	**7 000**	161 000	259 000	**420 000**
Q2 2016	--	9 000	**9 000**	294 000	243 000	**537 000**
Q3 2016	--	7 000	**7 000**	192 000	180 000	**372 000**
Q4 2016	--	5 000	**5 000**	82 000	139 000	**221 000**
Total			**371 000**	**1 052 000**	**2 014 000**	**3 066 000**

ROW = rest of the world.
[a] This figure includes US$ 170 million in previously deferred revenue in France.
Source: Bristol-Myers Squibb. Sales data for the first half of 2017 are not available.

TABLE A9-6.

Global originator sales of Viekira® and Zepatier® (US$ 000s), by quarter-year (Q)

	Viekira®			GZR/ELB (Zepatier®)		
	USA	**ROW**	**Total**	**USA**	**ROW**	**Total**
Q4 2014	48 000	--	**48 000**	--	--	**--**
Q1 2015	138 000	93 000	**231 000**	--	--	**--**
Q2 2015	227 000	158 000	**385 000**	--	--	**--**
Q3 2015	242 000	227 000	**469 000**	--	--	**--**
Q4 2015	197 000	357 000	**554 000**	--	--	**--**
Q1 2016	125 000	289 000	**414 000**	49 000	1 000	**50 000**
Q2 2016	87 000	332 000	**419 000**	107 000	4 000	**112 000**
Q3 2016	76 000	302 000	**378 000**	152 000	13 000	**164 000**
Q4 2016	54 000	257 000	**311 000**	180 000	49 000	**229 000**
Q1 2017	38 000	225 000	**263 000**	200 000	178 000	**378 000**
Q2 2017	26 000	199 000	**225 000**	256 000	261 000	**517 000**
Total	**1 258 000**	**2 439 000**	**3 697 000**	**944 000**	**506 000**	**1 450 000**

ROW = rest of the world.
Source: AbbVie; Merck.

Annex 10. Summary of patent information on selected direct-acting antivirals

This table provides a high-level overview of the patent situation of several DAAs in low- and middle-income countries, based on available data. [32]

	SIM		DCV		SOF		LDV		VEL		VOX		Viekira®						Zepatier®		Maviret®	
													dasabuvir		ombitasvir		paritaprevir		GZR	ELB	PIB	GLE
Argentina	G	G	F	F	F	F	F	F		F	F		G	F	F	F	F	F	F		F	F
ARIPO	G	F				G	F	F	F		F											
Bolivia											F										F	F
Brazil	F	F	F	F	F	F	F	F	F		F					F	F		F			F
Chile	F	G	G	G	G	F	F	F	F		F		F	F	F	F		F			F	F
China	G	G	G	G	G	F	G	F	G	F	F	F	G	F	G	G	G	G	G	F	G	F	G	F	G	F
China, Hong Kong SAR	G	G	G	G	F	F	F	F					F	F	F	F	G	F				
Colombia	G	G	G	G	G	G	G	G	G		F		F		G	G	G		G		G		F		F	
Costa Rica	F					F		F	F		F		F			F	F		F		F		F		F	
Dominican republic																			F		F		F		F	
EAPO	G	G	G	G		F	G	F	G	F	F	F		F	G	F	G	G	F		G		G	F	G	F
Ecuador	F	F				F	F	F	F		F		F		F	F	F	F	F		F		F		F	
Egypt	F	F		F				F	F		F		F		F	F			F		F		F		F	
El Salvador									G		F								F							
Ethiopia																										

[32] Source of data: WHO [51–55, 178–184].

	SIM	DCV	SOF	LDV	VEL	VOX	Viekira®			Zepatier®		Maviret®	
							dasabuvir	ombitasvir	paritaprevir	GZR	ELB	PIB	GLE
GCC	F F	F G	F	F		F	F	F F				F	F
Guatemala										F		F	F
Honduras										F			
India	F G	F G	G F	F F	F F	F	F	F F	F F	F	F	F	F
Indonesia	F	F	G F	F F		F	F	F				F	F
Iran (Islamic Republic of)													
Jordan	F F												
Lebanon													
Malaysia	G F	F	G F	F	F	F	F F	F F	F F	F		F	F
Mexico	G G	G G	G G	G F	F F	F	F F	F G	G G	F F	F F	F F	F F
Mongolia												F	F
Morocco			F	F	G	F				F	F		
Nigeria	G												
OAPI	G		G	G F	F	F							
Pakistan	F F		F	F F		F	F	F		G		F	F
Panama					F	F							F
Paraguay						F						F	F
Peru	G	G G		G F	F	F	F	F F	G F	G	F	F	F
Philippines	G G	F	G F	F	G	F	F G	G G	F	G	F	F	F
South Africa	G F	G G	G G	G F	F	F	G F	G G	G G			F F	G F
Thailand	F G	F F	F F	F F	F	F	F	F	F	F		G	F
Ukraine	G G		F	G F	G	F	F F	G G	G F	G		F	F
Uruguay	F F	F	F	F F	F	F F	F F	F F	F F			F	F
Venezuela		F F				F							F
Viet Nam	G F	F	F	F F	F	F	F	F F	F	F	F	F	F

G = patent(s) granted; F = patent(s) filed/pending. A blank cell means no information has been found or patent(s)/application(s) have been rejected. For each molecule, the first column (red font and bold) relates to the primary patent(s); the second column (black font) combines information for all other identified patents. Instances where one or more patents are granted and one or more others are filed or pending are marked "G" (granted).
ARIPO = African Regional Intellectual Property Organization (16 countries); EAPO = Eurasian Patent Organization (8 countries); OAPI = Organisation Africaine de la Propriété Intellectuelle (African Intellectual Property Organization) (16 countries).

Annex 11. Overview of countries included in voluntary licences

Country	SOF, LDV, VEL	DCV
Afghanistan		Yes
Algeria	Yes	Yes
Angola	Yes	Yes
Antigua and Barbuda	Yes	---
Azerbaijan	--	Yes
Bangladesh	Yes	Yes
Belize	--	Yes
Benin	Yes	Yes
Bhutan	Yes	Yes
Bolivia (Pluri-national State of)	Yes	Yes
Botswana	Yes	Yes
Burkina Faso	Yes	Yes
Burundi	Yes	Yes
Cambodia	Yes	Yes
Cameroon	Yes	Yes
Cape Verde	Yes	Yes
Central African Republic	Yes	Yes
Chad	Yes	Yes
Comoros	Yes	Yes
Congo, Republic	Yes	Yes
Cook Islands	Yes	Yes
Costa Rica	--	Yes
Côte d'Ivoire	Yes	Yes
Cuba	Yes	Yes
Democratic People's Republic of Korea	Yes	Yes
Democratic Republic of the Congo	Yes	Yes
Djibouti	Yes	Yes
Dominica	Yes	Yes
Dominican Republic	--	Yes
Ecuador	--	Yes
Egypt	Yes	---

Country	SOF, LDV, VEL	DCV
El Salvador	Yes	Yes
Equatorial Guinea	Yes	Yes
Eritrea	Yes	Yes
Ethiopia	Yes	Yes
Fiji	Yes	Yes
Gabon	Yes	Yes
Gambia	Yes	Yes
Georgia	--	Yes
Ghana	Yes	Yes
Grenada	--	Yes
Guatemala	Yes	Yes
Guinea	Yes	Yes
Guinea-Bissau	Yes	Yes
Guyana	Yes	Yes
Dominica	Yes	Yes
Dominican Republic	--	Yes
Ecuador	--	Yes
Egypt	Yes	---
El Salvador	Yes	Yes
Equatorial Guinea	Yes	Yes
Eritrea	Yes	Yes
Ethiopia	Yes	Yes
Fiji	Yes	Yes
Gabon	Yes	Yes
Gambia	Yes	Yes
Georgia	--	Yes
Ghana	Yes	Yes
Grenada	--	Yes
Guatemala	Yes	Yes
Guinea	Yes	Yes
Guinea-Bissau	Yes	Yes
Guyana	Yes	Yes
Lao People's Democratic Republic	Yes	Yes
Lesotho	Yes	Yes
Liberia	Yes	Yes
Libya	Yes	Yes
Madagascar	Yes	Yes
Malawi	Yes	Yes
Maldives	Yes	Yes
Mali	Yes	Yes
Marshall Islands	Yes	Yes
Mauritania	Yes	Yes
Mauritius	Yes	Yes
Micronesia (Federated States of)	Yes	Yes
Mongolia	Yes	Yes
Morocco	Yes	Yes
Mozambique	Yes	Yes

Country	SOF, LDV, VEL	DCV
Myanmar	Yes	Yes
Namibia	Yes	Yes
Nauru	Yes	Yes
Nepal	Yes	Yes
Nicaragua	Yes	Yes
Niger	Yes	Yes
Nigeria	Yes	Yes
Niue	--	Yes
Pakistan	Yes	Yes
Palau	Yes	Yes
Panama	--	Yes
Papua New Guinea	Yes	Yes
Paraguay	Yes	Yes
Philippines	Yes	Yes
Rwanda	Yes	Yes
Samoa	Yes	Yes
Sao Tome and Principe	Yes	Yes
Senegal	Yes	Yes
Seychelles	Yes	Yes
Sierra Leone	Yes	Yes
Solomon Islands	Yes	Yes
Somalia	Yes	Yes
South Africa		Yes
South Sudan	Yes	Yes
Sri Lanka	Yes	Yes
St Lucia	--	Yes
St. Vincent and the Grenadines	Yes	Yes
Sudan	Yes	Yes
Suriname	Yes	Yes
Swaziland	Yes	Yes
Syria	--	Yes
Tajikistan	Yes	--
Tanzania, United Republic of	Yes	Yes
Timor-Leste	Yes	Yes
Togo	Yes	Yes
Tonga	Yes	Yes
Tunisia	Yes	Yes
Turkmenistan	Yes	Yes
Tuvalu	Yes	Yes
Uganda	Yes	Yes
Uzbekistan	Yes	Yes
Vanuatu	Yes	Yes
Viet Nam	Yes	Yes
West Bank	--	Yes
Yemen	--	Yes
Zambia	Yes	Yes
Zimbabwe	Yes	Yes

Annex 12. The voluntary licence for sofosbuvir, ledipasvir and velpatasvir

Gilead's voluntary licence for SOF, LDV and VEL allows for the manufacturing of generic SOF, SOF/LDV and SOF/VEL, as well as the development of FDCs of SOF, LDV or VEL with other HCV medicines. Another positive feature of these voluntary licences is that they allow generic companies to supply to countries that are not included in the licence if those countries issue a compulsory licence.

There are concerns, however, about language in the licence that appears to restrict the ability of the licence-holders to procure and supply APIs, as well as supply finished formulations to countries that are not covered by the licence – even when there is no patent in those countries. Table A12-1 summarizes the options and questions regarding the supply to the "excluded" middle-income countries such as Brazil and Thailand by Indian generic companies that hold a licence.

TABLE A12-1.

Overview of options for supply of generics by Gilead licence-holders to countries excluded from the LICENCE

<table>
<tr><th></th><th>Patent(s) granted</th><th>Patent(s) pending</th><th>Patent(s) rejected but appealed</th><th>No patents (including final rejection)</th></tr>
<tr><td>Patent(s) granted</td><td>Yes if CL issued in importing country / CL for export issued in India</td><td>Yes if CL for export issued in India</td><td>Yes if CL for export issued in India</td><td>Yes if CL for export issued in India</td></tr>
<tr><td>Patent(s) pending</td><td>Yes if CL issued in importing country</td><td colspan="3" rowspan="3">Unclear situation, as national laws may not provide for issuing a CL on non-granted patents.
Also, when is there no “reasonable possibility” for Gilead to obtain a patent?</td></tr>
<tr><td>Patent(s) rejected but appealed</td><td>Yes if CL issued in importing country</td></tr>
<tr><td>No patents (including final rejection)</td><td>Yes if CL issued in importing country</td><td>Yes</td></tr>
</table>

“Yes” means generic companies that hold a licence for SOF, LDV, GS-5816 from Gilead will be able to supply. CL = compulsory licence.
= In these cases it is not clear whether generic companies that hold a licence will be able to supply to countries that are not included in the licence.

The countries included in Gilead’s voluntary licences (see Annex 11) will be able to buy generic versions of SOF, SOF/LDV and SOF/VEL from the licence-holders, regardless of whether patents are granted in these countries. If there are no patents, these countries may also buy from other generic manufacturers.

Countries not included in the licences can also buy from generic licence-holders if they issue a compulsory licence. When patents are pending – as is the case in a number of these countries (see Annex 10) – a compulsory licence would have to be issued on those pending patents in the concerned country and/or in India to enable Gilead licence-holders to supply. However, it is not clear whether national patent laws provide for the granting of compulsory licences on pending patents.

If there are no patents and no pending patent applications in a country outside the licence, the possibility of generic supply by the licence-holding companies in India will depend on the situation in India. Since some patents related to SOF reportedly have been granted in India [*240*] and several other patent applications are currently pending there [*50, 55*], India may have to issue a compulsory licence to enable licence-holders to supply. It remains to be seen how well this would work in practice.

Alternatively, if no patents are in force or when a compulsory licence has been issued, countries outside the licence could also buy generics from other (non-licence-holding) manufacturers. Otherwise countries could opt for local production, provided they can find a source of API[33] or are able to produce the API locally.

[33] The licence imposes conditions on API manufacturers that are similar to the conditions on finished products. In addition, APIs produced under the licence may be supplied only to generic manufacturers in India that hold a licence. Nevertheless, in practice it seems countries/generic manufacturers are able to obtain APIs.

Annex 13. Overview of generic versions of direct-acting antivirals

This annex provides an overview of generic versions of different DAAs known to be on the market in selected countries. Unless otherwise indicated, the products listed in this annex are registered by the relevant national regulatory authority.[34] This is not intended to be an exhaustive list

Generic versions of daclatasvir

Product name/brand name	Market authorization holder/supplier	Voluntary licence from BMS/MPP
Bangladesh		
Daclacee 60	Julphar Bangladesh Ltd	No
Daclavir	Beacon Pharmaceuticals Ltd	No
Dakla 60	Healthcare Pharmaceuticals Ltd	No
Dakovir-C 60	Beximco Pharmaceuticals Ltd	Yes
Virodacla	Incepta Pharmaceuticals Ltd	No
Egypt		
Augidacla	AUG Pharma	No
Clatazeva	Bristol-Myers Squibb-Egypt	Yes
Daclahepex	Global Pharmaceutical Industries	No
Daclatasvir-Uccma	United Company for Chemicals and Medical Preparations	No
Daclavir	Dawood Pharma Trade	No
Daclavirdin	Biothecary	No

[34] The mention of specific products or companies does not imply that they are endorsed or recommended

Daclavirocyrl	Marcyrl Pharmaceutical Industries	No
Daklanork	Mash Company for Pharmaceutical and Cosmetic (Mash Premiere)	No
Daktavira	European Egyptian Pharmaceutical Industries	No
Javidacla	Multicare Egypt for Pharmaceutical Industries	No
Zetaciver	Zeta Pharma for Pharmaceutical Industries (Zeta Pharm)	No
India		
DaciHep	Zydus Heptiza (Zydus Cadila)	Yes
Daclafab	Sun Pharma (Ranbaxy)	No
Daclahep	Hetero Healthcare Limited	Yes
DalsiClear	Abbott India Limited	No
HepCDac	Cipla Limited	Yes
HepCfix	Dr Reddy's Laboratories	No
MyDacla 60	Mylan Pharmaceuticals Ltd	No
Natdac	Natco Pharma Limited	Yes
Iran (Islamic Republic of)		
Daklibiox	Bakhtar Bioshimi Co.	No

Source (columns 1 and 2): Drug Administration Bangladesh, 31 July 2017; Egyptian Drug Agency, 31 July 2017; Medicines Patent Pool, 1 March 2017; Iran Food and Drug Administration, 24 June 2017; TREAT Asia/amfAR – The foundation for AIDS Research [241].
[a] Originator product.

Generic versions of sofosbuvir

Product name/brand name	**Market authorization holder/supplier**	**Voluntary licence from Gilead**
Bangladesh		
Buviren	Renata Limited	No
Hepacare 400 mg	Healthcare Pharmaceuticals Ltd	No
Hepcee	Julphar Bangladesh Ltd	No
Hopetavir	Incepta Pharmaceuticals Ltd	No
HopSo	Drug International Ltd	No

Soforal	Beacon Pharmaceuticals Ltd	No
Sofo-C	Aristopharma Limited	No
Sofomax	ACI Limited	No
Sofovir C	Beximco Pharmaceuticals Ltd	No
Soventa	Eskayef Bangladesh Ltd., Tongi	No
Sovir 400 mg	Unimed & Unihealth Manufacturers Ltd	No
Suvirus 400	Square Pharmaceuticals Ltd	No
Egypt		
Sovaldi[a]	IBIS Pharma	Distributor for Gilead in Egypt
Andohepasuvir	Al Andalous for Pharmaceutical Industries	No
Augispov	AUG Pharma	No
Averosofo	Averroes Pharma for Pharmaceutical Industries	No
Corcihepafect	Star Kamed for Medical Supplies	No
Geneduovir	Genesis Pharmaceuticals	No
Grateziano	European Egyptian Pharmaceutical Industries	No
Gratisovir	Pharco	No
Heterosofir	Pharmed Healthcare	Yes, for Egypt only
Hoforhep	Global NAPI Pharmaceuticals (GNP)	No
Kemisofo	Chemipharm Pharmaceutical Industries	No
Myhep	One Pharma Tech	No
Maglcbuvir	Magic Pharma	Yes, for Egypt only
Mpiviropack	Marcyrl Pharmaceutical Industries	No
Serinosprevir	Innovative Pharma	No
Sobosuvimec	Memphis	No
Sofocivir	Zeta Pharma for Pharmaceutical Industries (Zeta Pharm)	No
Sofodelevier	Al-Debeiky Pharma	No
Sofolanork	Mash Premiere	No
Sofolorocy	Pipeline Management guru	No
Sofomerase	Amoun Pharmaceutical Company	No
Sofoplatin	Dawood Pharma Trade	No
Soforoyal	Royal Link Pharma	No
Sofosbuvir- MUP	Medical Union Pharmaceuticals	No

Sofosbuvir-Biomed	Biomed pharmaceuticals	No
Sofosbuvir HR Inc	HR Inc. for Pharmaceutical Registration & Marketing	No
Sofosbuvir-IDI	International Drug Agency for Pharmaceutical Industry (IDI)	No
Sofosbuvir I.P.M.C	Innova Pharmaceutical Manufacturing Company	No
sofosbuvir naplex pharmaceuticals	Naplex Pharmaceutical	No
Sofosbuvir-pharco b international	Pharco B International-Egypt	No
Sofosbuvir - Pharmaserve Medical	Pharma Serve Medical	No
Sofosbuvir-uccma	United Company for Chemicals and Medical Preparations	No
Sofovirotal	Future Pharmaceutical Industries	No
Sofozav	Egyptian Company for Chemicals and Pharmaceutical Products	No
Sovaldia	IBIS Pharma	Yes
Tigaglor	Asia Mary Company	No
Virunator	Tabuk for Pharmaceutical Manufacturing Co.	No
India		
Sovaldi[a]	Mylan Pharmaceuticals Ltd	Distributor for Gilead in India
Cimivir	Biocon	Yes
Hepcinat	Natco Pharma Ltd	Yes
Hepcvir	Cipla Ltd	Yes
MyHep	Mylan Pharmaceuticals Ltd	Yes
Novisof	Wockhardt Ltd	No
Resof	Dr Reddy's Laboratories	No
Sofab	Ranbaxy Laboratories	Yes
Sofovir	Hetero Healthcare Ltd	Yes
SoviHep	Zydus Heptiza (Zydus Cadila)	Yes
Spegra	Emcure Pharmaceuticals Ltd	No
Viroclear	Abbott India Ltd	No
Virso	Strides Arcolab Ltd	Yes
Iran (Islamic Republic of)		
Hepacivir	Arena Life Science	No
Sobiovir	Bakhtar Bioshimi Co.	No

Sofira	Dr Abidi Pharmaceuticals	No
	Sobhan Medicine Trade Development Co.	No
Sofovir	Shari pharmaceutical	No
Pakistan		
Sovaldia	Ferozsons Laboratories Ltd	Distributor for Gilead in Pakistan; licence for Pakistan

Sources: Drug Administration Bangladesh, 31 July 2017; Egyptian Drug Agency, 25 January 2017; Gilead Sciences Inc. [190]; Iran Food and Drug Administration, 24 June 2017; TREAT Asia/amfAR – The foundation for AIDS Research [242].
[a] Originator product.

Generic versions of SOF/DCV

Product name/brand name	**Market authorization holder/supplier**	**Voluntary licence**
Bangladesh		
Darvoni	Beacon Pharmaceuticals Ltd	No
Iran (Islamic Republic of)		
SovodaK	Rojan	No

Sources: Drug Administration Bangladesh, 31 July 2017; Iran Food and Drug Administration, 24 June 2017.

Generic versions of SOF/LDV

Product name/brand name	**Market authorization holder/supplier**	**Voluntary licence from Gilead**
Bangladesh		
Dualvir	Aristopharma Limited	No
Duvir 90/400	Unimed & Unihealth Manufacturers Ltd	No
Harvocee	Julphar Bangladesh Ltd	No
Lesovir C	Beximco Pharmaceuticals Ltd	No
Sofomax Duo	ACI Limited	No
Sofoled	Eskayef Bangladesh Ltd, Tongi	No
Twinvir	Incepta Pharmaceuticals Ltd	No
Egypt		
Altcosodivir	Atco Pharma	No
Geneduovir	Genesis Pharmaceuticals	No

Harvonia	IBIS Pharma	Yes
Heterosofir plus 180/400	Pharmed Health Care	Yes, for Egypt only
Heterosofir Plus 90/400	Pharmed Health Care	Yes, for Egypt only
Ledisbuvir	Al Rowad for Pharmaceutical Industries	No
Mpiviropack plus	Marcyrl Pharmaceutical Industries	No
Myhep Lvir	One Pharma Tech	No
Napcovir	Napco Pharma	No
Neolipasvir	Riva Pharma	No
Orgopasvir	Organo Pharmaceutical and Chemical Industries (Organo Pharma)	No
Sofocivir Plus	Zeta Pharma for Pharmaceutical Industries (Zeta Pharm)	No
Sofolanork plus	Mash Company for Pharmaceutical and Cosmetic (Mash Premiere)	No
Sofosbuvir & Ledipasvir - Per Queen cosmetics	Perqueen Cosmetic	No
Sofosbuvir + Ledipasvir - Naplex Pharmaceuticals	Naplex Pharmaceutical	No
Sofoveravir	Averroes Pharma for Pharmaceutical Industries	No
Virosopasvir	United Company for Chemicals and Medical Preparations	No
India		
Cimivir L	Biocon Ltd	Yes
Hepcinat LP	Natco Pharma Ltd	Yes
HEPCVIR-L	Cipla Ltd	Yes
Ledifos	Hetero Healthcare	Yes
LediHep	Zydus Heptiza (Zydus Cadila)	Yes
Ledviclear	Abbott India Ltd	No
MyHep LVIR	Mylan Pharmaceuticals Ltd	Yes
Resof - L	Dr Reddy's Laboratories	No
SOFAB LP	Sun Pharma (Ranbaxy)	Yes
Iran (Islamic Republic of)		
Hepasbuvir Plus	Danesh Pharmaceutical Development Co.	No
Ledibiox	Bakhtar Bioshimi Co.	No
Ledisfovir	Shari pharmaceutical	No
Sobopasvir	Sobhan Medicine Trade Development Co.	No

Sources: Drug Administration Bangladesh, 31 July 2017; Egyptian Drug Agency, 31 July 2017; Gilead Sciences Inc. [*190*]; Iran Food and Drug Administration, 24 June 2017; TREAT Asia/amfAR – The foundation for AIDS Research [*243*].
[a] Originator product.

Generic versions of SOF/VEL

Product name/brand name	Market authorization holder/supplier	Voluntary licence from Gilead
Bangladesh		
Panovir	Incepta Pharmaceuticals Ltd	No
Sofosvel	Beacon Pharmaceuticals Ltd	No
Velsovir	Unimed & Unihealth Manufacturers Ltd	No
Velpacee	Julphar Bangladesh Ltd.	No

Sources: Drug Administration Bangladesh, 31 July 2017; Gilead Sciences Inc. [*190*].

Other generic direct-acting antivirals

Product name/brand name	Market authorization holder/supplier	Voluntary licence from Gilead
Egypt		
Neolipasvir	Riva Pharma S.A.E.	Glecaprevir 90 mg; LDV 90 mg; SOF 400 mg

Sources: Egyptian Drug Agency, 25 January 2017.

Annex 14. Experiences of buyers' clubs

An assessment was conducted of the efficacy and safety of generic DAAs legally imported through buyers' clubs into countries where treatment access is limited [*244*].

Overall, 1150 patients submitted results. Patients were from many different countries, but there were relatively high numbers from Australia, Eastern and Western Europe, New Zealand, South-East Asia, the USA and West Africa. Two Australian buyers' clubs helped a total of 772 people to source generic DAAs. Additionally, 154 persons obtained generics with assistance of a Chinese buyers' club, 224 obtained them via a Russian buyers' club and 100 obtained them through a buyers' club in South-East Asia.

Most patients were infected with HCV genotypes 1 or 3 (see Figure A14-1). The mean age was 44.4 years and the mean baseline HCV RNA was 6.8 log10 IU/mL. The choice of regimen and the length of treatment were determined on the basis of baseline RNA levels, HCV genotype and stage of fibrosis. The most commonly used treatments were SOF + DCV and SOF/LDV. For further details on patient characteristics and the treatments they used, see Table A14-1 and Figure A14-2.

TABLE A14-1.

Patient characteristics

	SOF or SOF + RBV (N = 100)	SOF + DCV (N = 545)	SOF/LDV (N = 502)
% male	79%	57%	57%
% with cirrhosis	16%	20%	16%
% Genotype 1	35%	31%	87%
% Genotype 3	46%	58%	4%
+ RBV	65%	7%	5%
treatment duration < 12 weeks	41%	66%	79%
treatment duration > 24 weeks	38%	21%	11%

Note: In addition, 2 persons received SOF/LDV + DCV and 1 person received SOF/VEL + RBV.

FIGURE A14-1.
PATIENTS BY GENOTYPE (G)

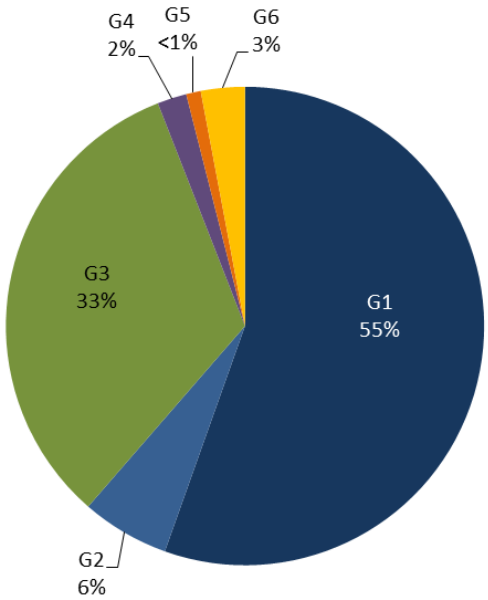
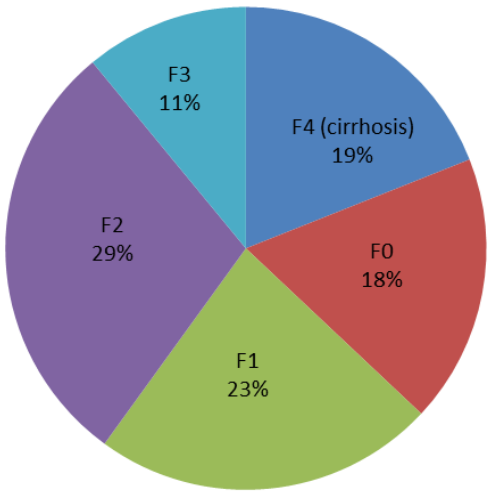


FIGURE A14-2.
FIBROSIS SCORES OF PATIENTS



As far as is known, the medicines supplied originated chiefly from various generic manufacturers in India (~45%) or from API suppliers in China (compounded by pharmacies in Australia, ~40%). The remainder originated from Bangladesh or Egypt.

Patient HCV RNA levels were evaluated prior to treatment, during treatment, at end of treatment and after treatment (SVR at 4, 12 and/or 24 weeks after the end of treatment). Based on currently available data, the percentage of patients with HCV RNA < LLoQ was 98% (263/269) at the end of treatment, 95% (652/683) at SVR4 and 92% (576/625) at SVR12 (see Table A14-2 and Figure A14-3).

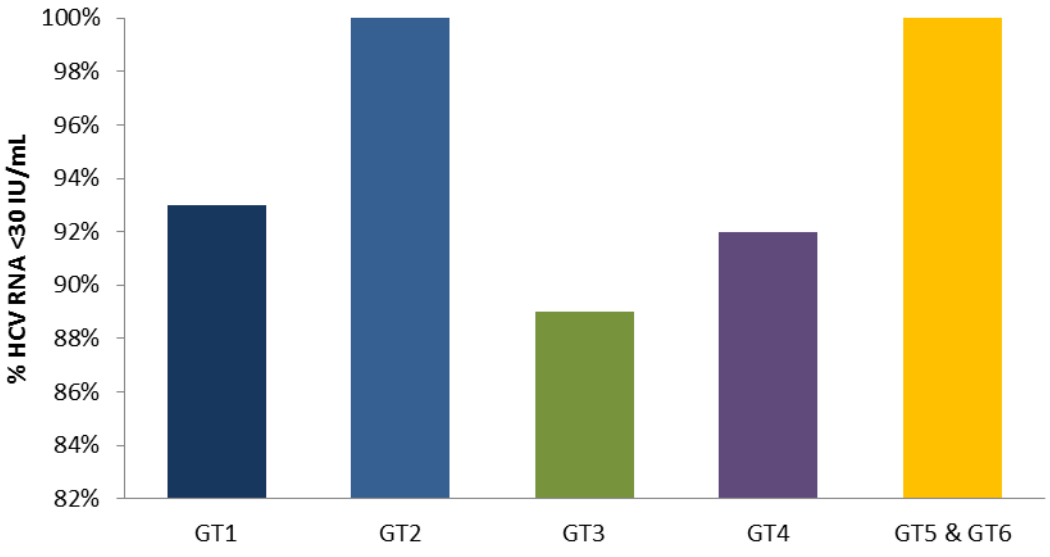
TABLE A14-2.

Treatment outcomes (HCV RNA < 25 IU/mL)

	SOF or SOF + RBV (N = 100)	SOF + DCV (N = 545)		SOF/LDV (N = 502)	
Rapid virological response (RVR)	92 % (55/60)	82 %	(305/374)	80 %	(296/370)
End of treatment (EOT)	98 % (39/40)	98 %	(121/123)	97 %	(102/105)
SVR 4	100 % (33/33)	94 %	(290/307)	96 %	(328/342)
SVR 12	92 % (24/26)	90 %	(256/285)	87 %	(296/341)

FIGURE A14-3.

SVR12 RATES BY GENOTYPE (GT), ALL REGIMENS



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