UNITAID

2015

# HEPATITIS C MEDICINES

## Technology and Market Landscape

FEBRUARY 2015

**UNITAID Secretariat**
**World Health Organization**
**Avenue Appia 20**
**CH-1211 Geneva 27**
**Switzerland**
**T +41 22 791 55 03**
**F +41 22 791 48 90**
**unitaid@who.int**
**www.unitaid.org**

**UNITAID is hosted and administered by the World Health Organization**



This report was prepared by Mike Isbell and Renée Ridzon (Ahimsa) and Karin Timmermans (UNITAID). All reasonable precautions have been taken by the authors to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall UNITAID or the World Health Organization be liable for damages arising from its use.

# CONTENTS

# Foreword

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

Much has changed since the first UNITAID scoping paper was published 16 months ago. The role of the two direct-acting antivirals that were first to market has significantly diminished, and both are being discontinued in the USA. Nine new direct-acting antivirals have been launched, though to date most are only available in a limited number of countries. This report takes stock of this rapidly changing market, where new products have the potential to become "blockbusters" almost overnight – but also risk becoming quickly outdated due to superior products entering the market.

Interferon- and ribavirin-free combinations are now on the market, at least for treatment of some genotypes of the hepatitis C virus. And while no short, simple pan-genotypic regimen is available yet for use in all patients (including cirrhotic patients and patients coinfected with HIV), the identification of such a regimen, which would be ideal for use in resource-limited settings, is progressing quickly.

Despite these advances, important challenges remain. The new medicines are very expensive; as a result, access is limited even in high-income countries. Access to these new medicines is virtually non-existent in the rest of the world.

Unaffordable prices for new hepatitis C medicines pose a major challenge, but one that can and should be addressed. UNITAID believes it is possible to create a virtuous circle of clearer demand, larger volumes, lower prices and sufficient funding to ensure that these medicines – which cure hepatitis C infection in a relatively short time – will be available to all who need them.

# Abbreviations

| | |
|---|---|
| **API** | Active pharmaceutical ingredient |
| **ART** | Antiretroviral therapy |
| **ARVs** | Antiretroviral medicines |
| **BOC** | Boceprevir |
| **CL** | Compulsory licence |
| **DAA** | Direct-acting antiviral |
| **DCV** | Daclatasvir |
| **FDC** | Fixed-dose combination |
| **HCV** | Hepatitis C virus |
| **HIV** | Human immunodeficiency virus |
| **LDV** | Ledipasvir |
| **Peg-IFN** | Pegylated interferon |
| **PEPFAR** | (United States) President's Emergency Plan for AIDS Relief |
| **Q** | Quarter(-year) |
| **RBV** | Ribavirin |
| **RNA** | Ribonucleic acid |
| **ROW** | Rest of the world |
| **SIM** | Simeprevir |
| **SOF** | Sofosbuvir |
| **SVR** | Sustained virological response |
| **TPV** | Telaprevir |
| **USA** | United States of America |
| **US FDA** | United States Food and Drug Administration |
| **WHO** | World Health Organization |

## Executive summary

**Hepatitis C virus (HCV) is a major global health problem.** With 80 – 150 million people worldwide chronically infected with the virus, the prevalence of HCV is higher than that of the human immunodeficiency virus (HIV). Worldwide, 4 – 5 million people are coinfected with HIV and HCV. Each year, 500 000 – 700000 people die of HCV-related liver disease, and evidence indicates that the HCV burden is increasing. While the HCV epidemic is global in scope, the HCV burden varies considerably between regions. There are six major genotypes of HCV, with genotypes 1 and 3 together accounting for more than three quarters of HCV infections.

**Efforts to treat HCV have historically been hampered by inadequate treatments.** Until recently, the standard treatment for HCV involved a combination of pegylated interferon (Peg-IFN) and ribavirin (RBV), with regimens lasting 24 – 48 weeks depending on the genotype. Weaknesses of Peg-IFN + RBV include suboptimal efficacy, poorer efficacy among patients with certain genotypes, and common, often severe side-effects that make the treatment intolerable for many patients. Diagnosis of HCV and treatment monitoring are also costly and complex, requiring multiple different tests, though this is in part attributable to the limitations of treatment with Peg-IFN and RBV.

**The development of direct-acting antivirals (DAAs) has dramatically improved HCV treatment prospects and altered the standard of care.** New DAAs that do not require Peg-IFN are being developed, with several receiving their first regulatory approval in late 2013 and 2014. A number of other DAAs are in development. These new DAAs are to be used in combinations. As measured by sustained virological response (SVR),[1] several DAA combinations appear to generate cure rates that approach or exceed 90%. Some of these combination regimens may have pan-genotypic efficacy, although the "ideal" regimen has not yet been established since data are currently not available for all genotypes and all patients groups (such as HIV/HCV coinfected patients or patients with cirrhosis). These DAAs can shorten treatment duration (in many instances to 12 weeks) and have fewer side-effects. They also have the potential to reduce the cost and complexity of diagnosing HCV.

**Widespread scale-up of DAAs in low- and middle-income countries is not currently feasible due to their very high prices.** The DAAs that have already received regulatory approval have exceptionally high prices, and even high-income countries struggle to cover treatment costs. Sofosbuvir has a commercial price of US$ 1000 per pill, or US$ 84 000 for a 12-week course of treatment in the USA. The prices of other DAAs are comparable. Some high-income countries have succeeded in negotiating price reductions, but these prices nevertheless remain far beyond those that would be affordable for widespread use in low- and middle-income countries. The Government of Egypt has negotiated a public-sector price of US$ 900 for a 12-week treatment course for sofosbuvir, but the number of doses available at this price is limited and it is unclear whether many other countries will be able to obtain similar prices. Virtually all sales of these medicines to date have occurred in high-income countries, with the USA and Europe together accounting for 98% of sales of sofosbuvir.

1 Sustained virological response means that there is no longer evidence of the presence of the virus in the patient's body.

**The high prices of DAAs are not related to the cost of production.** Assuming sufficient volumes, a recent academic analysis estimated that minimum production costs for a 12-week treatment course of several leading DAA combinations range from US$ 118 to US$193 per person.

**Patents pose a barrier to affordability and scale-up, although voluntary licences offer an avenue for generic production.** Patents for DAAs are likely to remain in force until at least 2025 and possibly beyond. In 2014, Gilead signed voluntary licences for two DAAs with seven Indian generic manufacturers, and Bristol-Myers Squibb, maker of other DAAs, also announced plans to issue voluntary licences. The Gilead licence covers 91 low- and middle-income countries, and includes half of all middle-income countries. However, it excludes the other 50% of middle-income countries, such as China which has the largest HCV epidemic in the world. The licensed manufacturers in India are currently developing generic DAAs; it is expected that generic equivalents will become available in late 2015 or 2016.

**Generic manufacturers will need substantial orders to achieve the economies of scale required to offer DAAs at affordable prices.** It is too early to obtain a firm market entry price for generic products, but most producers have indicated they would be able to offer sofosbuvir for less than US$ 900 for 12 weeks treatment (Gilead's price for sofosbuvir in Egypt). Prices of generic daclatasvir could be even lower. Achieving prices for generic versions of sofosbuvir and other DAAs that are sufficiently affordable to encourage scale-up of HCV treatment in low- and middle-income countries will, however, depend on volumes.

**The demand for DAAs among international donors and national governments remains uncertain.** No major international donor and few national governments have prioritized procurement of HCV medicines, in large part due to the high prices of DAAs. Sharp price declines – or the prospect thereof – will be needed to persuade donors and governments to make substantial purchases of DAAs.

**Additional factors potentially impede scale-up of DAAs.** Most people infected with HCV are undiagnosed, resulting in limited on-the-ground demand for HCV treatment. Capacity for diagnosis is limited in many low- and middle-income countries. Other factors that could hinder scale-up include possible regulatory delays, challenges associated with translating international recommendations into national treatment guidelines, and building capacity for HCV diagnosis and treatment.

**Addressing market weaknesses in the HCV treatment arena will require a combination of approaches that generate strong demand and address systemic issues.** Long-term investments in demand generation will be needed to improve diagnostic tools and strategies, enhance strategic data, advocate for robust funding by donors and national governments, and strengthen the ability of advocates to demand lower prices. Proof-of-concept studies will be required to demonstrate that HCV can be diagnosed and cured at minimal cost in low- and middle-income countries. At the same time that efforts focus on increasing demand, systemic issues (e.g. patent barriers, regulatory processes, timely generation of national treatment guidelines, health systems capacity) will need to be addressed. Once demand has been created, consideration should be given to bulk purchasing and other strategies to expedite uptake.

# 1. Introduction

UNITAID supports market-based interventions to improve access to medicines, diagnostics and preventive commodities for human immunodeficiency virus (HIV), tuberculosis and malaria. To help identify market-based interventions, UNITAID analyses the market of commodities of interest. These analyses, or landscapes, provide an overview of medicines on the market and in the pipeline, highlight critical market shortcomings and the underlying reasons for market failures, and identify potential strategies to correct them.

This landscape analysis surveys the current state of technologies for the treatment of hepatitis C virus (HCV), as well as market dynamics that affect the affordability and accessibility of HCV therapeutics. HCV treatment falls within the ambit of UNITAID's mission because it is a major HIV coinfection and a leading cause of morbidity and mortality among people living with HIV. Strategic Objective 3 of the UNITAID Strategy 2013 – 2016 specifically refers to viral hepatitis, notably hepatitis B and C.

Following a brief description of the methodology, this report assesses the public health problem of HCV infection. Section 3 provides an overview of current knowledge of the fast-evolving landscape of approved and experimental HCV treatments, comparing each to the ideal or target profile for an optimally effective and scalable HCV treatment regimen. Section 4 summarizes market dynamics associated with HCV treatments, including supply, demand and factors that affect the affordability, accessibility, uptake and sustainability of HCV treatments. Section 5 identifies weaknesses in the HCV treatment market, and the final section (6) proposes potential market interventions to enhance access to safe, effective and affordable HCV medicines.

# 2. Methodology

This landscape has been developed on the basis of an extensive desk review of published and grey literature, supplemented by interviews with key informants with knowledge of the state of the art of existing and pipeline technologies. Data and analysis are current as December 2014, unless otherwise indicated.

**Public health problem and global architecture:** These introductory sections review the HCV burden, summarizing the available data, and review some of the factors that need to be in place to enable treatment with the new HCV medicines in low- and middle-income countries. These sections were prepared by Mike Isbell and Renée Ridzon (Ahimsa).

**Technology landscape:** Tracy Swan developed the technology landscape material, including the tables and annexes 2 and 3. The material describing current and future products uses 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.

Figures 5 – 13 were prepared by Andrew Hill.

**Market landscape:** Karin Timmermans developed the market landscape, including the tables, figures and Annex 5. The section 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 sections on funding availability for procurement, demand impediments and other impediments to uptake were developed by Mike Isbell (Ahimsa).

**Market shortcomings and potential market interventions:** These sections were prepared by Mike Isbell and Renée Ridzon (Ahimsa) and Karin Timmermans (UNITAID).

Technical review and finalization of the overall report was conducted by Mike Isbell, Renée Ridzon (Ahimsa) and Karin Timmermans (UNITAID). The report was edited by David Bramley.

The following reviewers provided valuable input, comments and suggestions on all or part of the document: Isabelle Andrieux-Meyer, Peter Beyer, Jennifer Cohn, Charles Gore, Andrew Hill, Ellen 't Hoen, Yuanqiong Hu, Bernard Pécoul, Tracy Swan and Stefan Wiktor.

# 3. Public health problem

HCV is a serious health problem. With transmission patterns that overlap with those for HIV, HCV is several times more prevalent than 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 individuals.

Although transmission and pathogenesis of HCV are now well understood, important gaps in data undermine efforts to obtain a clear and timely epidemiological picture of the HCV epidemic. Less than half (49%) of countries reported having a national surveillance system in place for chronic HCV in 2013 *[1]*. Among countries that track hepatitis-related cases and deaths, 57 (53% of those reporting data systems, or 45% of countries overall) do not differentiate between the different types of hepatitis (i.e. A, B, C, D, E). Only about one third of countries regularly conduct serosurveys for viral hepatitis, with only 13 countries conducting such serosurveys annually *[1]*.

## Basic facts about HCV

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, transmission is 10 times more efficient for HCV than for HIV *[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 the use of enzymes and other means, HCV replicates itself in order to infect additional liver cells.

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

Infected individuals 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 *[3]*.

The World Health Organization (WHO) has identified the primary modes of HCV transmission *[2]*:

- *Drug injecting:* The sharing of injecting equipment during drug use is a primary cause of HCV transmission in many countries, including in a growing number of resource-limited settings.
- *Health care:* Reuse or poor sterilization of needles, syringes or other medical equipment is also a major source of HCV transmission.
- *Blood:* In countries where blood donations are not routinely screened for bloodborne pathogens, blood transfusions or other blood products may lead to HCV transmission.
- *Sexual activity:* HCV transmission during penile-vaginal intercourse is uncommon, although HCV is transmitted between men who have sex with men, especially among those who are HIV-positive *[4]*.
- *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 HIV (17 – 25 per 100) *[5]*. Unlike HIV, HCV cannot be transmitted through breast-milk *[2]*.

HCV transmission has also been linked to tattooing and body piercing when the equipment used is not sterile *[5]*. 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, although efforts to develop a preventive vaccine are ongoing.

## Global health burden associated with HCV

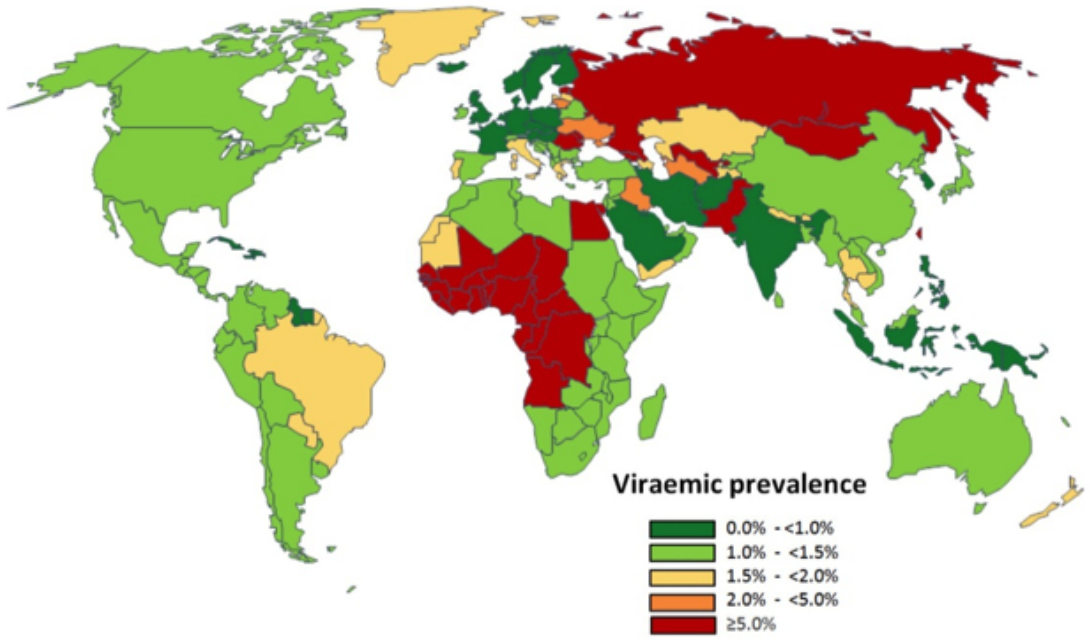
Global estimates of the number of persons with HCV infection vary considerably, reflecting the lack of data from many countries on the burden of HCV disease. Globally, HCV antibody prevalence is estimated to be between 1.6% and 2.8% as compared with a global prevalence for HIV of 0.8% *[6 – 8]*. The estimates of the number of persons with chronic (i.e. life-long) HCV infection are also uncertain and range between 80 million and 150 million *[2, 7]*.

HCV is a major source of morbidity and mortality, and this burden is increasing. According to the Global Burden of Disease Study, an estimated 500 000 persons died in 2010 from HCV-related liver disease, and by 2013 the estimated number of deaths increased to 700 000 *[9, 10]*. For individuals with chronic HCV infection, 5–20% will develop cirrhosis (typically, over a period of two or three decades) and 1–5% will die of liver cancer *[4]*. Between 1990 and 2013, of all cancers, only liver cancer caused by HCV increased substantially (by 125%) *[10]*.

Certain populations are especially heavily affected by HCV. Globally, two in three (67%) people who inject drugs are infected with HCV *[5]*. HCV levels are also elevated in many populations of HIV-positive men who have sex with men; in Switzerland, for example, HCV incidence among men who have sex with men is now higher than among people who inject drugs *[11]*.

The burden of HCV varies considerably between regions (Figure 1) though data are limited. In low- and middle-income countries, HCV prevalence reportedly ranges from 1.2% in tropical Latin America to 3.8% in Central Asia. In addition, HCV prevalence exceeds 3% in East Asia (3.7%), North Africa and Middle East (3.6%) and South Asia (3.4%), with HCV prevalence approaching 3% in Eastern Europe (2.9%) and western sub-Saharan Africa (2.8%). It is estimated that at least 50 million people are infected with HCV in both East Asia and South Asia, with an additional 11 million HCV-infected people living in South-East Asia. North Africa and the Middle East are home to 11 million people with HCV infection *[5]*.

**Figure 1. Global prevalence of HCV**

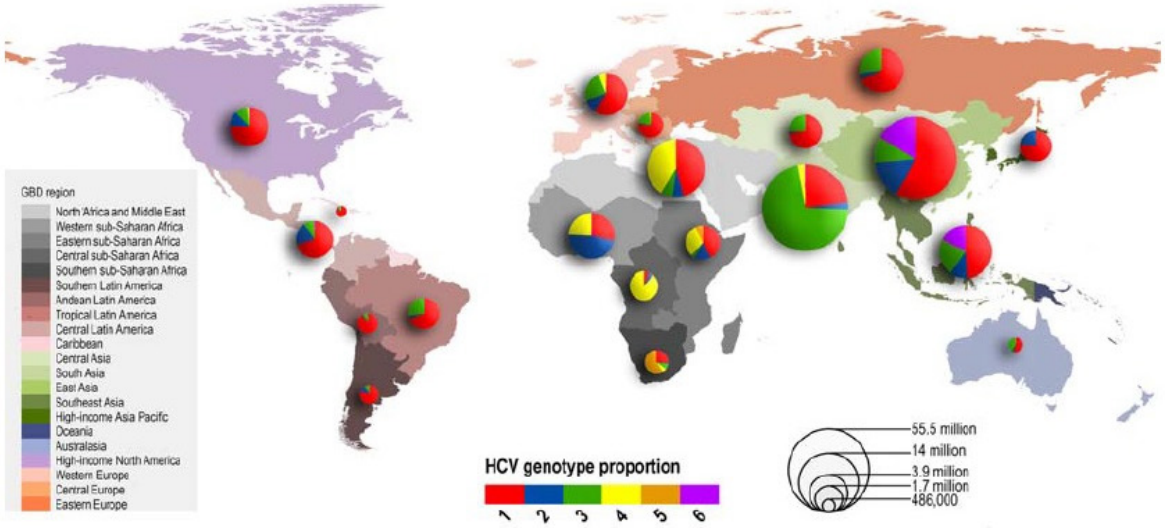



*Source:* Gower E et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of hepatology. 2014;6(1Suppl):S45–57.

Patterns of transmission vary across the globe. In high-income countries, HCV is typically transmitted through use of certain medical equipment (e.g., kidney dialysis, endoscopy) and during injecting drug use *[12],* although recent years have seen a notable increase in transmission among HIV-positive men who have sex with men *[13].* In resource-limited settings, health-related interventions, such as blood transfusions and injections of medicines, are an important source of HCV transmission. Frequent injections, especially where infection control practices are suboptimal, facilitate rapid HCV transmission; in Egypt, for example, an estimated 9.8% of the population is infected with HCV *[5].*

There are six primary genotypes of the virus. Genotypes 1 and 3 are the most prevalent, accounting for 46.2% and 30.1% of HCV cases worldwide, respectively *[14].* Together, genotypes 2, 4 and 6 represent 22.8% of HCV cases, while genotype 5 accounts for less than 1% *[14].* Within regions, substantial genetic variation is apparent (Figure 2).

**Figure 2. Global distribution of HCV genotypes 1–6**



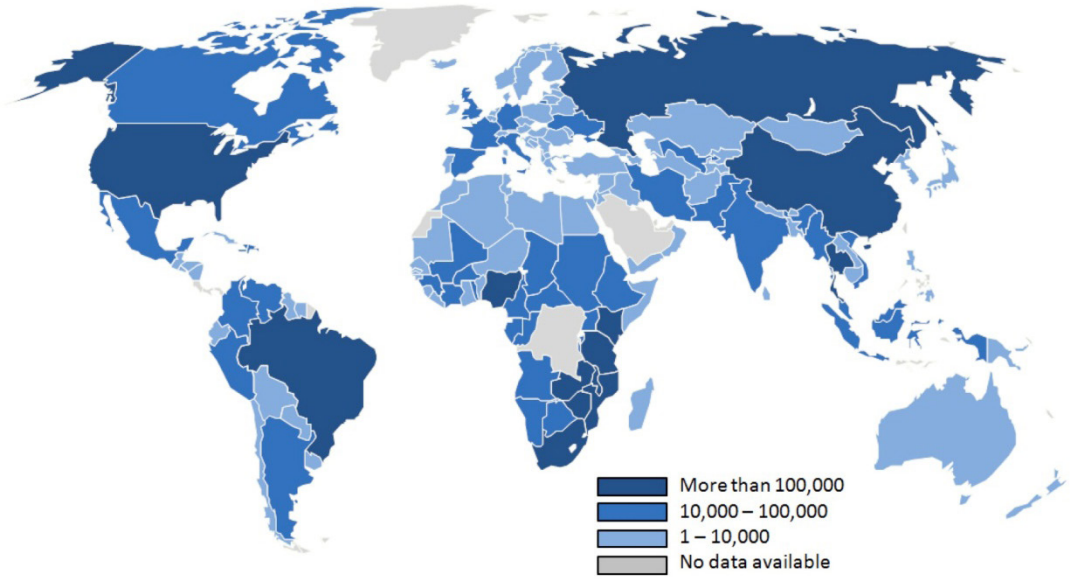

*Source:* Messina JP et al. Global distribution and prevalence of hepatitis C virus. Hepatology. 2015;1(1):77–87.

## HIV/HCV coinfection

The HCV and HIV epidemics interact in several ways. Both viruses, for example, have similar transmission routes. In addition, pre-existing HIV infection increases susceptibility to HCV acquisition *[5];* HIV-positive men who have sex with men appear 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.

Worldwide, 4 – 5 million people are coinfected with HIV and HCV *[5].* Among geographical populations of individuals who acquired HIV through injecting drug use, it is common to find that HCV prevalence exceeds 90% *[4, 15, 16].* More than a dozen countries in multiple regions are home to at least 100 000 people with HIV/HCV coinfection (Figure 3).

**Figure 3. Estimated number of HIV/HCV coinfected people**




*Source:* Center for Disease Analysis.

In high- and upper-middle-income countries, an estimated 20% and 25%, respectively, of people living with HIV are coinfected with HCV. Somewhat lower coinfection rates are estimated for lower-middle-income (15%) and low-income (10%) countries *[17],* although data are limited. Low- and middle-income countries account for an estimated 45% of all coinfected people *[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 in settings 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 and mortality in this population, even among people receiving antiretroviral therapy *[28 – 34].* For individuals who develop cirrhosis, coinfection increases by six-fold the risk of hepatic decompensation, resulting in substantially lower survival among the coinfected in comparison to people infected with HCV alone *[35, 36].*

Ironically, even as antiretroviral therapy has dramatically improved HIV-related clinical prospects, its scale-up has increased the incidence of HCV-related disease 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 antiretroviral therapy is widespread, HCV-related end-stage liver disease is now a leading cause of death among people living with HIV *[31, 32, 34].* 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 the low- and middle-income countries where HIV treatment has more recently been expanded, it can be anticipated that increased longevity associated with antiretroviral therapy will also lead to increased incidence of HCV-associated end-stage liver disease in those countries.

# 4. Factors that can facilitate the uptake of new HCV medicines

For a new treatment to become available for use in resource-limited settings, a multi-step process is typically required.

## 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 USA's 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 simeprevir (SIM) was first approved in Japan. Approval by such regulatory bodies allows a drug to be marketed only in the country (or countries) over which the particular agency has jurisdiction (e.g. the USA for the USFDA). However, approval by a stringent regulatory body can prove influential more widely.

For HIV medicines, the USA has typically required that a drug be approved by the USFDA before it may be purchased with USA funds for international health assistance, and the USFDA has created a tentative approval procedure for this purpose.

## Role of WHO

WHO is the global agency of most immediate importance with respect to the introduction of new medical innovations in resource-limited settings. WHO strongly influences practice 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 guidelines dealing with the treatment of HCV *[5].* These *Guidelines for the screening, care and treatment of persons with Hepatitis C infection* provide guidance on such matters as HCV screening, administration of HCV treatment, clinical monitoring, operational and implementation issues, and considerations for specific populations. Acknowledging that the HCV treatment landscape is rapidly evolving, WHO indicated in 2014 that the guidelines would be regularly updated to take account of a rapidly evolving standard of care.
- *Model List of Essential Medicines List:* The WHO Essential Medicines List contains more than 400 medicines and is revised every two years *[37].* The list provides guidance to resource-limited countries on priority medicines for procurement and use. Any party may submit an application to WHO for inclusion of a product on the Essential Medicines List, with the WHO Expert Committee taking into account such factors as disease prevalence, safety and efficacy in determining whether to include a new drug on the list. Pegylated interferon alpha and ribavirin are included in the current (18th) version of the list *[37].* Applications for the inclusion of several direct-acting antivirals (DAAs) (notably daclatasvir, SIM, SOF, and the fixed-dose combination ledipasvir/SOF) have been submitted to WHO[2] and will be considered in the upcoming revision of the Essential Medicines List in April 2015.
- *Prequalification:* Prequalification by WHO is often a prerequisite for donors to use their funds to purchase a particular drug. To be eligible for prequalification, medicines or diagnostics must be on the Essential Medicines List or be included in WHO treatment guidelines. Using information submitted by manufacturers, WHO undertakes a comprehensive evaluation of the quality, safety and efficacy of a medical product under consideration for prequalification. WHO's list of prequalified drugs is primarily intended to guide procurement decisions by United Nations agencies but over time it has become influential with respect to procurement decisions by national governments and donors. In September 2014, WHO issued for the first time a specific invitation for expressions of interest from manufacturers and suppliers of medicines for HCV and hepatitis B as well as HIV-related medicines for product evaluation with a view to WHO prequalification.

2 See: http://www.who.int/selection_medicines/committees/expert/20/applications/en/ (accessed 18 January 2015).

- *Price transparency:* In December 2014, WHO added a section on price information of HCV medicines to its database for prices of HIV medicines.
- *Patent information*: WHO published reports on the patent status of seven new and pipeline HCV medicines in August 2014 *[38 – 44].* 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.

## National action

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 *[45]* or under-resourced.

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. In 2013, 64 countries (or 51% of those providing information to WHO) had clinical guidelines in place for the treatment of HCV, with treatment guidelines addressing HIV/HCV coinfection in 35 of these countries *[1]*.

In 2013, 47 countries (or 37% of respondents) reported the existence of a national strategy focused exclusively or primarily on HCV control, with 93 countries (74%) reporting that a viral hepatitis control programme was in place *[1]*. In 37 of the 47 countries with national HCV strategies, these frameworks address HCV treatment and care *[1]*. Among the 93 countries with a national HCV control programme, 55% reported HCV-related activities specifically focused on people who inject drugs and 47% reported activities focused on people living with HIV *[1]*.

National patent laws and decisions of the national patent office to grant or reject patents related to HCV medicines also impact on access to HCV medicines. This is addressed below in Section 4 on "Market landscape".

# 5. Technology landscape

## Overview

Until recently, 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 is undetectable HCV ribonucleic acid (RNA) 12 – 24 weeks after completing a course of treatment; this is called sustained virological response (SVR). SVR rates for the combination Peg-IFN + RBV were suboptimal (~55%), with even lower cure rates reported for coinfected persons. In addition, the combination of Peg-IFN and RBV is expensive compared with other priority therapeutics in resource-limited settings. It is also associated with debilitating and often intolerable side-effects that require monitoring, which can be complex and taxing for both patients and clinicians *[46 – 49]*.

Recent years have seen profound advances in the medical management of HCV infection with the development of new medicines (direct-acting antivirals or DAAs). The new DAAs can cure HCV infection, as measured by SVR. A host of studies has found that SVR reduces AIDS-related, liver-related and non-AIDS-related morbidity and mortality among individuals with HIV/HCV coinfection, even when liver disease is advanced *[28, 50, 51]*.

In 2011, researchers established proof of concept for an interferon-free cure with oral drugs *[52]*. Emergence of a series of DAA regimens with cure rates exceeding 90%, for both mono-infected and coinfected patients, has changed the standard of care for HCV *[53-56]*. These newer regimens are safer, more tolerable, simpler and shorter than Peg-IFN + RBV, and they require less intensive monitoring. Targeting various stages in the HCV replication process, DAAs come in a number of classes – namely protease inhibitors, nucleoside/tide polymerase inhibitors, NS5A inhibitors, and non-nucleoside polymerase inhibitors.

With a robust pipeline in place for HCV treatments, further research advances are anticipated in the near future, with expectations that one or more DAAs or combinations thereof that meet the target product profile for an optimally effective HCV cure will be available in the not too distant future. The ideal treatments would yield cure rates of 90% or more for both mono-infected and coinfected patients, across all genotypes as well as in people with cirrhosis. They should be available for use along with WHO-recommended antiretroviral medicines (ARVs) and should be suitable for delivery in existing HIV treatment programmes in resource-limited settings.

Although progress on the HCV therapeutic front has been transformative, access to existing DAAs is virtually non-existent in most resource-limited settings. In addition to delays associated with the multiple steps required for new drugs to become available in developing countries, the high prices attached to these new DAAs make them currently unaffordable for many countries.

## Treatments for HCV infection

This section summarizes the available safety and efficacy data on existing and pipeline medicines for the treatment of HCV, including both the now-superseded standard of care (Peg-IFN + RBV) and the recently launched and emerging DAAs.

### 1. Pegylated interferon and ribavirin

Neither interferon (IFN, an infection-fighting cytokine produced with recombinant DNA technology) nor RBV (a nucleoside analogue) was originally developed for treatment of HCV. INF activates an immune response that defends against HCV infection. RBV interferes with viral replication. When combined with RBV, IFN cures twice as many patients as IFN alone *[57]*.

Interferon alpha 2a and 2b have been commercially available since 1986. Generic RBV is available at a daily cost of US$0.30. Treatment with interferon alpha 2a and 2b requires injections three times per week.

The first version of (Peg-IFN was launched in 2001. By enhancing the duration of IFN in the body, Peg-IFN reduced the number of injections required to one per week. WHO treatment guidelines recommend

Peg-IFN in combination with RBV *[5],* and in 2013 WHO added Peg-IFN as a complementary medicine (i.e. a drug that is "…not necessarily affordable, or for which specialized care facilities or services may be needed") to its Model List of Essential Medicines *[37].* In 2013, 55% and 58% of countries reported inclusion of Peg-IFN and RBV, respectively, on their national essential medicines list *[1].*

Although Peg-IFN + RBV served as the cornerstone of HCV treatment for more than a decade, the combination is far from ideal. First, while lower than those for DAAs, prices for Peg-IFN + RBV are nevertheless high. In addition, treatment efficacy is suboptimal, with only slightly more than half of the people who start therapy achieving SVR *[48, 49, 58].* Efficacy of Peg-IFN + RBV declines as patients have more liver damage (and thus have a more urgent need for treatment). Efficacy is also notably lower for patients coinfected with HIV compared to individuals infected with HCV alone.

Peg-IFN + RBV requires extensive monitoring of safety and efficacy and quantification of the HCV viral load at multiple time points, but also renders genotyping and assessment of the severity of liver disease necessary. This is complex and requires the availability of a number of diagnostic tests.

SVR rates with Peg-IFN + RBV are notably higher for genotypes 2 and 3 than for genotypes 1 and 4 (there is only limited data on efficacy for genotypes 5 and 6). Efficacy is especially poor in coinfected persons, with the most prevalent genotype 1 (14 – 29%). SVR rates and treatment duration for Peg-IFN + RBV are summarized by genotype in Table 1.

**Table 1. SVR: by HCV genotype and HIV status, PEG-IFN + RBV** *[47-49, 58-65]*

| Genotype | T Duration | % SVR, HCV | % SVR, HIV/HCV |
|---|---|---|---|
| 1 | 48 weeks | 49% (meta-analysis, LMIC treatment programmes)<br>~44% (clinical trials) | 24.5% (meta-analysis; observational cohort data)<br>14–29% (clinical trials) |
| 2/3* | 24 weeks in HCV mono-infection; usually 48 weeks in HIV/HCV | 59% (meta-analysis, LMIC treatment programmes)<br>~80% (clinical trials) | 59.8% (meta-analysis; observational cohort data)<br>genotype 2: 68.3%; genotype 3: 56.5% (clinical trial) |
| 4 | 48 weeks | 49% (meta-analysis, LMIC treatment programmes)<br>77% (clinical trials; limited data and small sample size) | 24.5% (meta-analysis; observational cohort data)<br>28% (retrospective analysis; two multicentre studies) |
| 5 | 48 weeks | 55–87% (clinical trials; limited data and small sample size) | **No data** |
| 6 | 48 weeks | 66–86% (clinical trials; limited data and small sample size) | **No data** |

*SVR in genotypes 2 and 3 are often reported together, although PEG-IFN and RBV are more effective for genotype 2 than for genotype 3.
LMIC = low- and middle-income countries.

As Table 1 illustrates, the duration of treatment with Peg-IFN + RBV is quite long (24 or 48 weeks, depending on the HCV genotype).

In addition, treatment with Peg-IFN + RBV is commonly associated with side-effects, such as influenza-like symptoms, neutropenia, anemia, thrombocytopenia, psychiatric events and worsening of existing, or occurrence of *de novo,* autoimmune disorders (e.g. type 1 diabetes, thyroid dysfunction, psoriasis, rheumatoid arthritis) *[66, 67].* Almost one in four (24%) patients enrolled in four clinical trials was unable to tolerate Peg-IFN + RBV *[68].* According to a survey of 697 physicians from 29 countries, fear of side-effects and concerns regarding treatment duration represent critical barriers to effective HCV treatment *[69].* Because of the high prevalence of side-effects, many HCV-infected people are unable to take Peg-IFN + RBV due to pre-existing medical conditions.

Peg-IFN + RBV's side-effects are especially severe for coinfected patients, who are more likely than mono-infected patients to experience weight loss, anaemia, neutropenia and thrombocytopenia *[70-73]*. The HIV antiretrovirals didanosine and zidovudine are contraindicated during HCV treatment with Peg-IFN + RBV *[72, 74, 75]*.

In recent years, Peg-IFN + RBV has been combined with other HCV treatments such as HCV protease inhibitors or SOF. These combinations have generated higher cure rates compared with the traditional treatment of Peg-IFN + RBV alone, although side-effects and contraindications associated with these older medicines reduce the utility of such combinations.

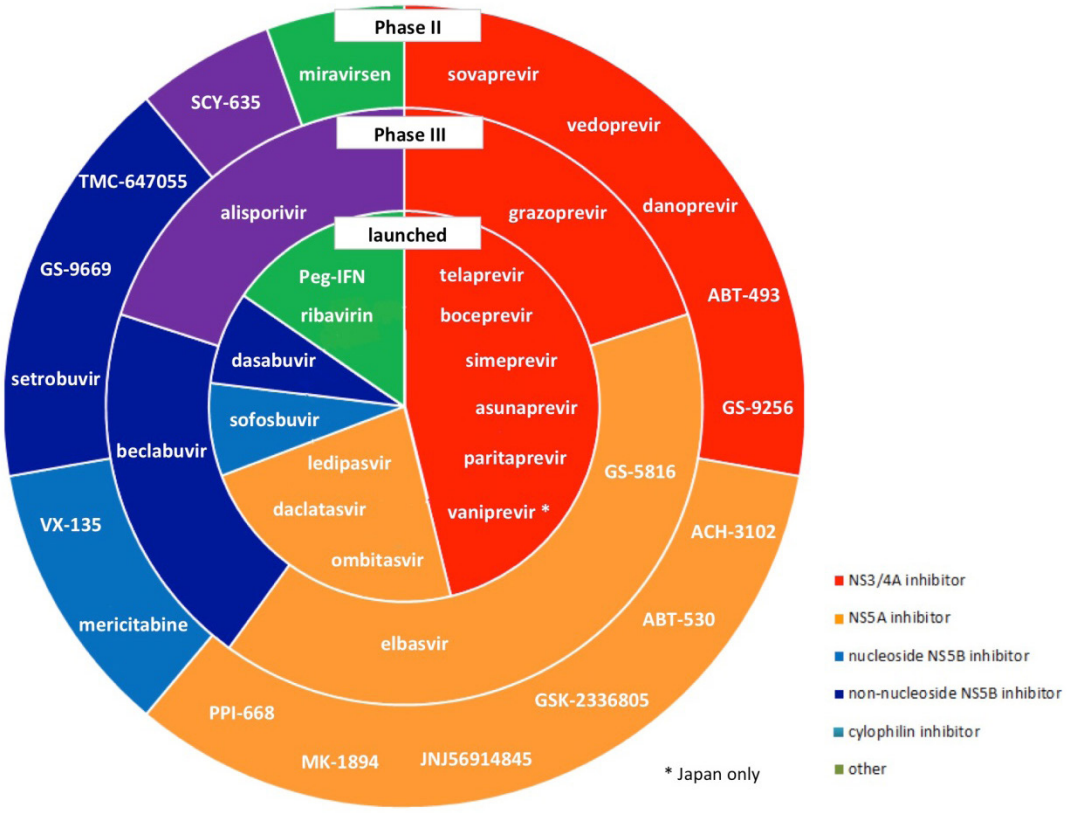
## 2. Direct-acting antivirals

The emergence of numerous DAAs in recent years has allowed the development of highly effective, IFN- and 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.

This section initially analyses individual DAAs within the various anti-HCV drug classes, organized according to the component of the HCV replication cycle targeted by the drugs. Within each class of drugs, the discussion first examines medicines that have already been approved by at least one regulatory body and then describes the current state of the research pipeline. The section closes with a discussion of currently available and in-development combination DAA regimens.

There is, however, an important caveat: developments in the field of HCV are taking place rapidly, which suggests that the standard of care may continue to evolve. As shown in Figure 4 and Annex 1, a robust pipeline exists for DAAs and is transforming the HCV therapeutic landscape rapidly. As a result, achieving the goal of having a safe, tolerable, highly effective, pan-genotypic and user-friendly HCV regimen is coming into sight.

**Figure 4. Overview of DAAs on the market and in the pipeline (phase II and III).**




*Source:* UNITAID.

### a. HCV protease inhibitors

HCV protease inhibitors prevent the release of proteins that are essential to viral replication. The emergence of HCV protease inhibitors represented the first substantial step away from exclusive reliance on Peg-IFN + RBV, although the earliest HCV inhibitors were used in combination with Peg-IFN + RBV.

As a class, HCV protease inhibitors have significant limitations. Current HCV protease inhibitors are not pan-genotypic, although there are hopes that at least two candidates in the pipeline will offer therapeutic benefits across all genotypes. In genotype 1a, the resistance profile and SVR rates are suboptimal with protease inhibitor-based regimens. HCV protease inhibitors also have a propensity for drug – drug interactions and cannot be co-administered with many commonly-used medications, including some antiretroviral drugs.

Despite these drawbacks, protease inhibitors play an important role in several promising combination regimens. However, their limitations diminish their value for patients with HIV/HCV coinfection.

#### *Boceprevir and telaprevir*

In 2011, the USFDA and the EMA approved the first DAAs – the protease inhibitors boceprevir (BOC) and telaprevir (TPV). Approval of these medicines represented an important breakthrough for HCV treatment, increasing SVR rates to about 70% for genotype 1 and shortening treatment duration for early responders who were HIV-negative, non-cirrhotic, treatment-naïve or relapsers *[76, 77]*. Similar SVR rates were reported in coinfected patients after 48 weeks of treatment *[78, 79]*. However, these medicines have now been superseded by safer, simpler, more effective and more tolerable anti-HCV agents.

There are several limitations to BOC and TPV. Neither drug is pan-genotypic, with efficacy limited to genotype 1. Both drugs must be used in combination with Peg-IFN + RBV, and each is less effective and more toxic when administered in people with cirrhosis *[80]*.

Substantial infrastructure requirements are associated with BOC-based or TPV-based regimens. Both are administered as response-guided therapy, with treatment duration in HIV-uninfected, non-cirrhotic, treatment-naïve or relapsers[3] ranging from 4 to 48 weeks. Intensive safety monitoring is needed, with up to eight clinic visits and at least 50 laboratory tests required for a course of treatment *[81]*, limiting the viability of BOC- and TPV-based treatment in resource-limited settings. In the USA, a major New York City hospital reported a median cost per SVR with TPV-based treatment of US$ 189 000 *[82]*.

BOC- and TPV-based regimens are also not user-friendly. These therapies require two or three daily doses, must be taken with food, and interact with many commonly prescribed medications, including some antiretroviral medicines. Side-effects are common, including gastrointestinal adverse events, itching, serious or life-threatening rash, hypersensitivity and haemorrhoids. BOC and/or TPV also have side-effects which add to those already associated with Peg-IFN and RBV, especially in patients with cirrhosis *[80]*.[4]

As a result of the complexity and toxicity of BOC- and TPV-based regimens, real-world SVR rates are much lower than those reported by clinical trials. Among treatment-naïve patients, SVR rates of about 55% are reported, with half of patients who initiate BOC- or TPV-based treatment outside clinical trials discontinuing the regimens prior to cure *[80]*.

In 2013, almost 20% of countries reported having BOC and/or TPV on their list of essential medicines *[1]*. With newer, superior, IFN-free regimens now available, the 2014 WHO guidelines now "suggest", rather than "recommend", the use of BOC or TPV *[5]*. Leading professional groups – such as the American Association for the Study of Liver Diseases, the Infectious Disease Society of America, and the European Association for the Study of Liver Disease – no longer recommend BOC or TPV *[83]*. Both products are being withdrawn from the market in the USA *[84, 85]*.

3 A person is said to be "treatment-naïve" if he or she has never received therapy with a licensed HCV medicine. A person with HCV who initially had treatment-associated SVR and later has detectable virus is said to have "relapsed".

4 See also prescribing information for BOC at http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf and for TPV at http:///www.accessdata.fda.gov/drugsatfda_docs/label/2012/201917s007lbl.pdf (accessed 29 January 2015).

***Simeprevir***

In 2013, SIM, the first once-daily HCV protease inhibitor, was approved in Japan, Canada and the USA. Developed for use in combination with Peg-IFN + RBV in genotypes 1 and 4, SIM generated cure rates above 80% after 24 weeks (12 weeks of SIM + Peg-IFN + RBV, followed by 12 weeks of Peg-IFN + RBV) *[86-89]*. Citing high-quality evidence, WHO's 2014 HCV treatment guidelines recommend SIM with Peg-IFN and RBV for treating genotypes 1b and 1a (without the Q80 mutation[5]) in lieu of Peg-IFN + RBV alone *[5]*. Although originally developed to be used in combination with Peg-IFN + RBV, SIM has been successfully evaluated in other combinations, leading the USFDA in October 2014 to approve the IFN-free, RBV-free, 12 – 24 week combination of SIM + SOF for the treatment of genotype 1.

Like its fellow HCV protease inhibitors BOC and TPV, 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.

***Asunaprevir***

Japan approved asunaprevir (in combination with daclatasvir) for the treatment of HCV in 2014.[6] In October 2014, however, Bristol-Myers Squibb withdrew its USFDA application for this combination, citing the rapid evolution of HCV treatments. Asunaprevir requires frequent liver enzyme monitoring.

***Paritaprevir***

Paritaprevir was approved by several stringent regulatory bodies in late 2014. It is co-formulated with ombitasvir and boosted with ritonavir. This fixed-dose combination (FDC) forms as part of AbbVie's "3D" combination (See the discussion below of the "3D" combination.)

***Vaniprevir***

In September 2014, vaniprevir, an oral twice-daily protease inhibitor was approved in Japan. Merck has since announced that it plans to make vaniprevir available only in Japan.[6]

***Pipeline for HCV protease inhibitors***

Development of a number of HCV protease inhibitors has stalled or has been halted due to side-effects, with reported adverse events including cardiotoxicity or hepatoxicity for various candidates. In June 2014, Boehringer Ingelheim discontinued development of faldaprevir and announced plans to withdraw pending marketing applications for the drug, citing the imminent availability of IFN-free treatment options.

Second-wave and next-generation HCV protease inhibitors appear to hold promise as they are more potent, less prone to resistance, more convenient (most are once-daily) and more tolerable than earlier drugs of this class. In particular, there are hopes that Gilead's Phase I candidate, GS-9857, and AbbVie's Phase II drug, ABT-493, will have pan-genotypic efficacy.

Table 2 summarizes the state of the pipeline for HCV protease inhibitors that are currently in development.

5 This mutation, which was found to reduce treatment efficacy in clinical trials, is common among patients infected with genotype 1a (48% in clinical trials) but infrequent among persons with genotype 1b. See: http://hepatitiscnewdrugresearch.com/olysiosimeprevir-resistant-variant-q80k.html (accessed 29 January 2015).

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

**Table 2. HCV protease inhibitors in development** *[80, 83, 90-93]* [7]

| Compound and Company | Phase | Dose | Cautions | Comments |
|---|---|---|---|---|
| **ABT-493** AbbVie | II | Under study; QD | | Multi-genotypic activity; active against resistant variants (in vitro)<br>In development and co-formulated with ABT-530, an NS5A inhibitor |
| **ACH-1625** (Sovaprevir) Achillion Pharmaceuticals | II | ≤200 mg QD | Partial clinical hold remains for multiple-dose studies in healthy volunteers; dose limited to 200 mg in HCV patients | |
| **Danoprevir/r** Hoffman-LaRoche | II | 100/100 BID | Stalled in phase II; BID-dosing and ritonavir boosting; less effective in genotype 1a | Also studied in genotype 4 |
| **GS 9451** Gilead Sciences | II | 80 mg QD | | Only one trial, SYNERGY (NIAID-sponsored) |
| **Asunaprevir** BMS | III; USA approval sought only for "TRIO" regimen; expected in 2015 | 100 mg BID with daclatasvir; 200mg BID in triple regimen | BID dosing; propensity for drug–drug interactions; some ALT elevations | Primary interest is use in BMS "TRIO" regimen (with daclatasvir (NS5A inhibitor) and beclabuvir (non-nucleoside polymerase inhibitor) |
| **Grazoprevir (MK-5172)**/ MK-8742 (elbasvir) Merck | III; approval expected in 2015/2016 | 100 mg/50 mg QD | Propensity for drug–drug interactions; currently, can be used with raltegravir-based ART only | FDC: coformulated with MK-8742 (NS5A inhibitor); studies underway in genotypes 1, 2, 4, 5 and 6, ± RBV; with SOF in G 1,2, 3 |

Note: BMS = Bristol-Myers Squibb; QD = once a day; BID = twice a day; ALT = alanine aminotransferase (a liver enzyme); ART = antiretroviral therapy.

### b. Nucleoside/tide polymerase inhibitors

SOF is currently is the only approved nucleotide polymerase inhibitor. Additional nucleoside/tide polymerase inhibitors are in the drug development pipeline.

#### *Sofosbuvir*

SOF is a once-daily, pan-genotypic nucleoside polymerase inhibitor that is rapidly becoming the backbone of HCV treatment. 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. In Phase III trials, less than 3% of participants in SOF-based, IFN-free arms were discontinued as a result of adverse events, with fatigue and headache representing the most commonly reported adverse events *[94 – 97]*.[8]

SOF must be used in combination with other anti-HCV medicines. WHO treatment guidelines include a strong recommendation, based on high-quality evidence, for SOF-RBV (with or without Peg-IFN) for treating HCV genotypes 1, 2, 3 and 4 *[5]*. Data are limited for genotypes 5 and 6. As the discussion below regarding combination regimens indicates, recent clinical trials have yielded evidence of the clinical value of other SOF-based combinations.

7 See also prescribing information for Olysio®: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s001lbl.pdf (accessed 29 January 2015).
8 See also Sovaldi® prescribing information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf (accessed 29 January 2015).

SOF has been studied in treatment-naïve and treatment-experienced patients, in individuals with mono-infection and coinfection, and in patients with and without cirrhosis. SOF has also been evaluated in a variety of combinations, including with Peg-IFN + RBV, RBV alone and in a wide array of IFN- and RBV-free combinations. SOF-based combinations are typically achieving cure rates in excess of 90% (see below), although studies indicate occasional variations in efficacy depending on the genotype. Data are not currently available across all genotypes for all SOF-based combinations.

***Pipeline for nucleoside/tide polymerase inhibitors***

A number of other nucleoside/tide polymerase inhibitors are in development. Efforts to develop additional drugs in this category have encountered considerable challenges. Most notably, several investigational nucleoside/tide polymerase inhibitors have been discontinued due to toxicity concerns, including renal and cardiac toxicity, gastrointestinal adverse events, lymphopenia, neutropenia and hepatoxicity.

Among nucleoside/tide polymerase inhibitors, the furthest along in development is mericitabine, although its performance (with or without IFN and other DAAs) has been lackluster. As a result, mericitabine appears to be stalled in Phase II.

VX-135 showed initial promise, but USFDA placed a clinical hold on the 200 mg dose after elevated liver enzymes were reported at the 400 mg dose. SVR rates from a Phase IIa trial of VX-135 (73% in the 100 mg arm and 83% in the 200 mg arm) were lower than those reported for other regimens in development *[98]*. Vertex announced plans to out-license VX-135 in 2014.

Other molecules in early stages of development include ACH-3422 (Achillion), as well as IDX-20963 and IDX-21437 (Merck); safety and efficacy information on these compounds is eagerly awaited. In November 2014, Janssen acquired Alios BioPharma, including their two HCV nucleotide polymerase inhibitors – AL-335 (about to enter Phase I testing) and AL-516 (in preclinical development).

Table 3 summarizes the current state of development of non-SOF nucleoside/tide polymerase inhibitors.

**Table 3. HCV Nucleoside/tide polymerase inhibitors in development** *[99]*

| Compound and Company | Phase | Dose | Cautions | Comments |
|---|---|---|---|---|
| **ACH-3422** Achillion | I | Under study; QD | | In vitro, increased potency against HCV genotype 3 |
| **MK-3662** (formerly IDX 21437) Merck | I/II | Under study; likely to be 300 mg QD | Limited data; likely to be developed only with Merck's other DAAs | |
| **Mericitabine** Roche | II | 1000 mg BID | Appears to be stalled in phase II; it does not significantly increase SVR | |
| **VX-135** Vertex | II | <200 mg QD | USFDA put clinical hold on 200 mg dose; Vertex seeking to out-license this drug | |

Note: QD = once a day; BID = twice a day.

**c. NS5A inhibitors**

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. Studies of NS5A inhibitors have primarily enrolled patients with genotypes 1, 2, 3 and 4, with more limited data available regarding people with genotypes 5 and 6.

NS5A inhibitors are usually quite potent, although they do not have a high genetic barrier to resistance. Baseline resistance to NS5A inhibitors is common (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, especially when treatment has been extended to 24 weeks *[100 – 103]*. Combining an NS5A inhibitor with a potent drug with a superior resistance profile improves treatment outcomes, with cure rates of some such combinations approaching 100%. However, patients who are unsuccessfully treated with combination regimens that include NS5A frequently have post-treatment resistance, the long-term consequences of which remain unclear *[104]*.

Most NS5A inhibitors are taken once daily. NS5A inhibitors may interact with some antiretroviral medicines. For instance, for daclatasvir-containing HCV regimens, dose adjustments are required for coinfected patients who are taking efavirenz, ritonavir-boosted atazanavir or certain other ARVs.

NS5A inhibitors are critical components of safe, pan-genotypic, highly effective and tolerable regimens, in part because some NS5A inhibitors do not require RBV. However, additional research is needed to optimize NS5A inhibitor-based regimens since available data do not clearly indicate which NS5A inhibitor is superior or how best to delay or overcome drug resistance.

#### *Daclatasvir*

Daclatasvir (DCV) has received regulatory approval from the European Union and Japan in 2014. The first NS5A inhibitor ever approved, DCV has been studied with Peg-IFN + RBV and as well as with DAAs from each class. Although DCV was developed to be used in combination with RBV, it is likely to be used in other ways in future. To date, combinations of DCV with SOF (now in Phase III testing) appear most promising (an issue explored in greater depth in the discussion below of DAA combination regimens).

#### *Ledipasvir*

Ledipasvir (LDV) is currently available only as an FDC with SOF (brand name Harvoni®). The once-daily single tablet regimen has been approved for use in genotype 1 in Canada and the USA and for use in genotypes 1 and 4 in Europe (see the discussion below of DAA combinations for more details). Although preclinical data indicated that LDV was less potent in genotype 3 than in genotypes 1, 4 and 6, adding RBV in Phase II trials produced SVR rates exceeding 80% in genotype 3 *[105 – 107]*.

#### *Ombitasvir*

Ombitasvir was approved by several stringent regulatory bodies in November and December 2014; it is available as an FDC with ritonavir-boosted paritaprevir. (See the discussion below of AbbVie's "3D" combination.)

#### *Pipeline for NS5A inhibitors*

Table 4 summarizes the state of the research pipeline on NS5A inhibitors as of November 2014. As the table indicates, approval of additional NS5A inhibitors is expected in 2015 – 2016. Of particular interest is Gilead's investigational compound GS-5816, which is believed to be pan-genotypic.

**Table 4. HCV NS5A inhibitors in development** *[108–115]*

| Compound and Company | Phase | Dose | Cautions | Comments |
|---|---|---|---|---|
| MK-8408<br>Merck | I | Under study; QD | | Pan-genotypic; active against resistant variants (in vitro) |
| ABT-530<br>AbbVie | II | Under study | Propensity for drug–drug interactions | Pan-genotypic; active against resistant variants (in vitro); studied in genotype 3 with ABT-450/r ± RBV |
| **ACH-3102**<br>Achillion Pharmaceuticals | II | 50 mg QD | When used with sovaprevir (protease inhibitor) and ribavirin, high treatment failure rate In genotype 1a | Pan-genotypic; active against resistant variants (in vitro)<br>In genotype 1b, Il28B CC, 38% (3/8) achieved SVR-24 after 12 weeks of ACH-3102 and ribavirin; in genotype 1, 100% (12/12) achieved SVR-12 after 8 weeks of ACH-3102 + SOF |
| **JNJ56914845**<br>Janssen | II | 30 or 60 mg QD | Not pan-genotypic; less potent against genotypes 2 and 3 | |
| **IDX-719 (samatasvir)**<br>Idenix/Merck | II | 25, 50, 100 or 150 mg QD | Idenix was sold to Merck in mid-2014; the future of samatasvir is uncertain (Merck has other NS5a inhibitors in development) | Pan-genotypic, but less active against genotype 2 (in vitro); studied in genotypes 1 and 4 |
| **GS-5816/**sofosbuvir<br>Gilead Sciences | III; approval expected in Q4 2015 or Q1 2016 2016 | 100mg QD | Propensity for drug–drug interactions | FDC: coformulated with sofosbuvir (nucleotide polymerase inhibitor) |
| **Elbasvir (MK-8742)** /Grazoprevir (MK-5172)<br>Merck | III<br>Approval expected in 2016 | 50 mg QD | Propensity for drug–drug interactions | FDC: coformulated with MK-5172 (protease inhibitor); trials in genotypes 1, 2, 4, 5 and 6 ± RBV; with sofosbuvir in genotypes 1, 2 and 3 |

Note: QD = once a day.

### d. Non-nucleoside polymerase inhibitors

Non-nucleoside polymerase inhibitors generally play a supporting role in HCV therapy. They are normally combined with at least one compound from another anti-HCV class in IFN-free regimens. Most non-nucleoside polymerase inhibitors are effective only against genotype 1, potency varies, and their genetic barrier to resistance ranges from low to moderate. Little information is currently available regarding possible drug – drug interactions or their effectiveness in patients with advanced cirrhosis. All non-nucleoside polymerase inhibitors are taken twice a day, with the exception of Gilead's candidate GS-9669, which is taken once daily.

#### *Dasabuvir*

Dasabuvir is a non-nucleoside polymerase inhibitor that received initial regulatory approval in late 2014 for use in combination with ombitasvir/paritraprevir/ritonavir in AbbVie's "3D" combination. In a Phase II trial, the addition of dasabuvir increased the cure rate for the combination regimen from 89% to 96% in genotype 1. Patients with genotype 1a and some patients with genotype 1b must take RBV with the "3D" regimen.

***Pipeline for non-nucleoside polymerase inhibitors***

Numerous candidate non-nucleoside polymerase inhibitors have been discontinued for lack of efficacy, toxicity or both. However, some candidates from this class are in development, including Bristol-Myers Squibb's beclabuvir (BMS 791325), which may receive initial regulatory approval in 2015 or 2016 as part of a three-drug combination for use in genotype 1. Table 5 summarizes the state of research for unapproved candidates in this class as of November 2014.

**Table 5. HCV non-nucleoside polymerase inhibitors in development** *[116–119]*

| Compound and Company | Phase | Dose | Cautions | Comments |
|---|---|---|---|---|
| **GS 9669**<br>Gilead Sciences | II | 500 mg QD | | Future of this drug is unclear |
| **Setrobuvir (ANA 595)**<br>Hoffman-LaRoche | II | 800 mg BID loading dose; 400 mg BID | Appears stalled in Phase II | Future of this drug is unclear |
| **TMC647055**<br>Janssen | II | 450 mg or 600 mg QD | Boosted with low-dose ritonavir (30 mg) | |
| **Beclabuvir (BMS 791325/** DCV/ASV)<br>Bristol-Myers Squibb | III; approval expected 2015/ 2016 | 75 mg BID | Twice-daily regimen; propensity for drug–drug interactions | FDC; coformulated with daclatasvir (NS5A inhibitor; 30 mg) and asunaprevir (protease inhibitor, 200 mg) in ribavirin- free genotype 1 regimen<br>Activity against genotypes 1,3, 4, 5 and 6 (in vitro); studied only in genotype 1 |

Note: QD = once a day; BID = twice a day.

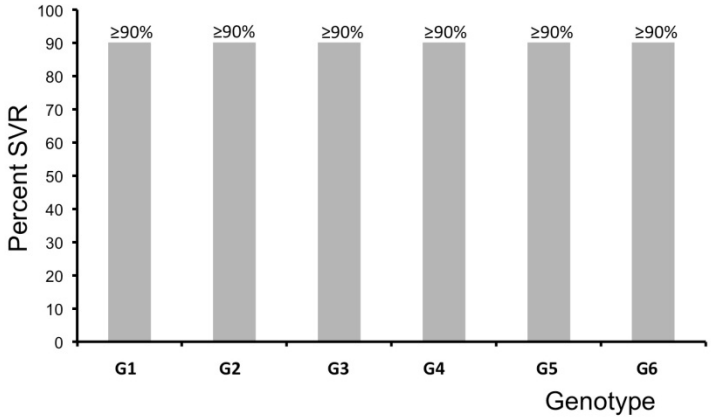
## 3. Target product profile

To assess existing HCV therapies as well as those in the development pipeline, it is helpful to identify the ideal, or target, profile for HCV drugs or regimens for use in resource-limited settings. The ideal HCV treatment would be:

- *Safe and tolerable*, definitely IFN-free and preferably RBV-free (to avoid side-effects associated with RBV), and safe for use in pregnant women,[9] children, HIV/HCV coinfected individuals and patients with cirrhosis.
- *Universal or 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. unlikely that HCV develops resistance to the drug(s) with proper treatment adherence), and associated with SVR rates of at least 80% and ideally 90% in all genotypes (see Figure 5).
- *Simple*, including 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 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 and their communities.
- *Stable* at both high and low temperatures.

9 To be safe for use in pregnant women, HCV treatment regimens have to be RBV-free since RBV is embryotoxic and teratogenic.

**Figure 5. Target product profile: SVR of the ideal treatment**




At this stage it is difficult to identify best-in-class DAAs, since they are developed only as parts of regimens. Moreover, clinical data are often limited to certain genotypes. Meanwhile, the development of the best pan-genotypic combination has been relatively slow, partly due to the commercial focus on in-house regimens which has effectively limited the collaborative approaches needed to develop the regimens and FDCs that appear to hold the most promise.

Pan-genotypic regimens, once they exist, will simplify procurement and delivery of HCV treatment, especially if the duration of treatment does not vary by genotype. Safe and efficacious pan-genotypic regimens will also simplify the complex diagnostic algorithm.

SOF, a once-daily, pan-genotypic nucleotide polymerase inhibitor, is poised to become the backbone of HCV treatment. Protease inhibitors are less desirable for treating coinfected patients in low- and middle-income countries, as they are not pan-genotypic, are likely to have drug – drug interactions with ARVs and other commonly used medicines, and may require RBV use, especially for genotype 1a. Non-nucleoside polymerase inhibitors, which are primarily active against genotype 1 and require twice-daily dosing, play a lesser role. Optimal regimens combine nucleoside/tide polymerase inhibitors and NS5A inhibitors, as this combination is typically pan-genotypic and potent, requires once-daily dosing, and generally does not include RBV.

## 4. Combination regimens versus target product profiles

As in the case of antiretroviral therapy for HIV infection, optimal treatment for HCV infection involves the combination of anti-HCV compounds of different classes. This section describes combinations of the individual medicines reviewed above and assesses them on the basis of currently-available data against the target profile discussed above.

Although, SOF has emerged as the backbone of HCV treatment, it is likely that scientific understanding of optimal HCV treatment will continue to evolve. Table 6 summarizes current information with respect to the efficacy of SOF-based regimens across different subtypes and in different patient populations. For detailed information, see Annex 2.

Annex 3 includes a table summarizing how regimens of key DAAs (including those that have been approved, as well as especially promising regimens currently in later stages of development) that are discussed below fare in comparison to the criteria in the target product profile can be found in.

**Table 6. Summary of SVR of sofosbuvir-based regimens**

| | SVR in HCV mono-infection | SVR in HIV/HCV coinfection | Treatment duration |
|---|---|---|---|
| Genotype 1 | 68–100% | 76–100% | 8–24 weeks |
| Genotype 2 | 91–100% | 88% | 12–24 weeks |
| Genotype 3 | 89–100% | 89% | 12–24 weeks |
| Genotype 4 | 86–100% | 84% | 12–24 weeks |
| Genotype 5* | 100% | No data | 12 weeks |
| Genotype 6* | 96–100% | No data | 12 weeks |

* Small sample size; 1 person with genotype 5 and 35 people with genotype 6.

### a. Approved sofosbuvir-based combination regimens

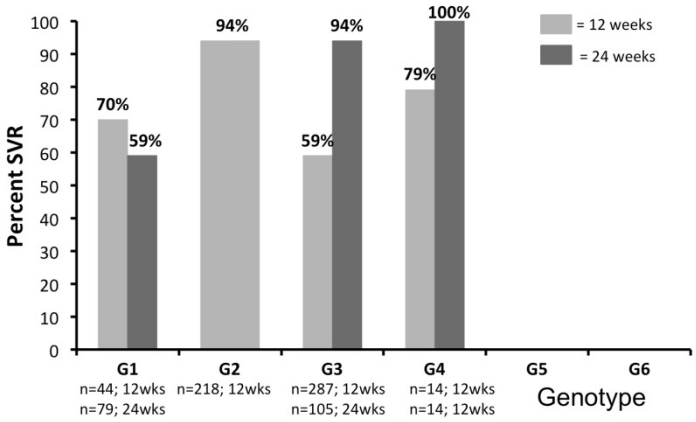
Three SOF-based regimens have been approved. They generally achieve high cure rates, although lower SVR rates have been found in patients with cirrhosis and certain genotypes. Because not all SOF-based combinations have been evaluated across all genotypes, there remain gaps in the evidence regarding their effectiveness in some patient populations, although available evidence indicates that SOF-based regimens tend to be pan-genotypic.

#### *Sofosbuvir + ribavirin*

In its initial approval of SOF for the treatment of HCV in 2013, the USFDA advised that SOF should be used in combination with either RBV or Peg-IFN + RBV. The combination of SOF + RBV is still relatively complex; 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.[10] Fatigue and headache were the most common adverse events reported by clinical trials participants who received SOF + RBV. RBV can cause birth defects and fetal death and is contraindicated in pregnancy. Women and their partners should avoid pregnancy for six months after stopping RBV.

Cure rates for SOF + RBV are generally lower than those reported for combinations of DAAs, especially at 12 weeks (Figure 6). In genotypes 3 and 4, a 24-week regimen is more effective than the 12-week regimen. SOF + RBV appears to be roughly equally effective in coinfected patients as treatment in mono-infected patients *[55]*.

**Figure 6. Sofosbuvir + RBV: SVR after 12 and 24 weeks**




*Sources* of data: G1: SPARE, QUANTUM, VALENCE; G2: POSITRON, VALENCE, FISSION; G3: VALENCE; G4: Ruane et al. *[120]*.
Notes: G = genotype. No bar means no data (not "zero efficacy").

10 See prescribing information for Copegus: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021511s023lbl.pdf (accessed 29 January 2015).

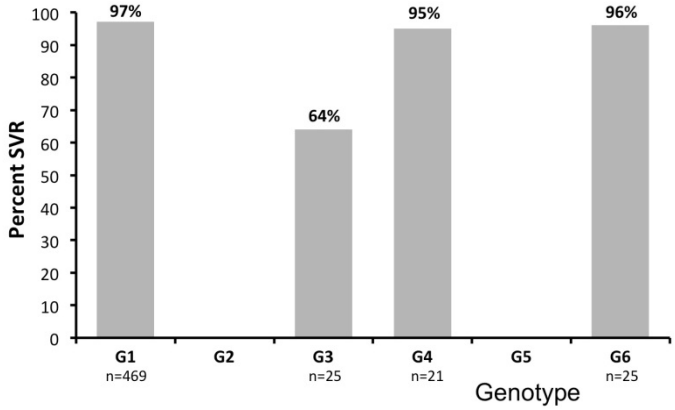
An important limitation to SOF + RBV is its suboptimal efficacy for patients with genotype 1, the most prevalent genotype globally *[53, 97]*.

SOF + RBV is also less effective for people with advanced fibrosis or cirrhosis, especially in genotypes 1 and 3. While the overall SVR for SOF + RBV in the PHOTON-2 trial was 88%, it fell to 65% in patients with cirrhosis *[53]*. In the SPARE trial, patients with genotypes 1 and pre-cirrhosis or cirrhosis (METAVIR F3 or F4) were four times more likely to relapse than patients with mild-to-moderate liver damage; among trial participants with more severe liver disease, more than half (54%) relapsed.

***Sofosbuvir/ledipasvir***

The FDC of SOF and LDV (brand name Harvoni®) makes for a safe, effective, one-pill, once-daily treatment for genotype 1. The fact that this FDC does not need to be used with RBV in genotype 1 makes its side effect profile superior to that of SOF + RBV. Cure rates for SOF/ledipasvir have topped 95% in gentoypes 1, 4 and 6, although trial populations were relatively small for genotypes 4 and 6. Lower SVR rates have been found for patients with genotype 3, who need to use SOF/LDV with RBV (Figure 7) *[94, 105 – 107, 121]*.

**Figure 7. Sofosbuvir/ledipasvir: SVR after 12 weeks**




*Sources* of data: G1: LONESTAR, ION-1, ION-3, ELECTRON, SYNERGY; G3: ELECTRON-2; G4: SYNERGY; G6: Gane et al. *[106]*.
Notes: G = genotype. No bar means no data (not "zero efficacy").

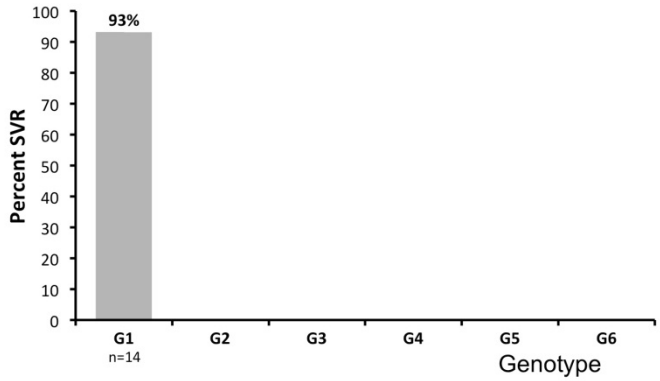
A small trial involving coinfected patients also found that SOF/ledipasvir is safe and effective, and other studies in coinfected populations are underway or planned. Encouragingly, a study of SOF/ledipasvir in treatment-experienced HCV mono-infected patients with cirrhosis yielded an SVR of 86% after 12 weeks and 100% after 24 weeks *[94]*.

Standard therapy with SOF/ledipasvir lasts 12 weeks, although treatment can be shortened to eight weeks for some patients. The combination SOF/ledipasvir can be used with some WHO-recommended ARVs, although toxicity monitoring may be required.

***Sofosbuvir + simeprevir***

In the Phase II COSMOS trial, SOF + SIM (with or without RBV) achieved SVR rates above 90% among null responders and people with compensated cirrhosis after 12 weeks of therapy (Figure 8) *[122]*, prompting the USFDA to approve the IFN- and RBV-free combination of SOF + SIM for the treatment of genotype 1. The standard regimen of SOF + SIM lasts 12 weeks, although it is extended to 24 weeks for patients with cirrhosis. Efficacy data are not currently not available for patients with genotypes 2 – 6 and this combination has not been studied in HIV/HCV coinfected patients.

**Figure 8. Sofosbuvir + simeprevir: SVR after 12 weeks**




*Sources* of data: G1: COSMOS Cohort 2 – includes null-responders, all patients F3/F4
Notes: G = genotype. No bar means no data (not "zero efficacy").

**b. Additional SOF-based combinations**

As part of the rapidly evolving landscape for HCV treatment, additional SOF-based combinations are actively being explored.

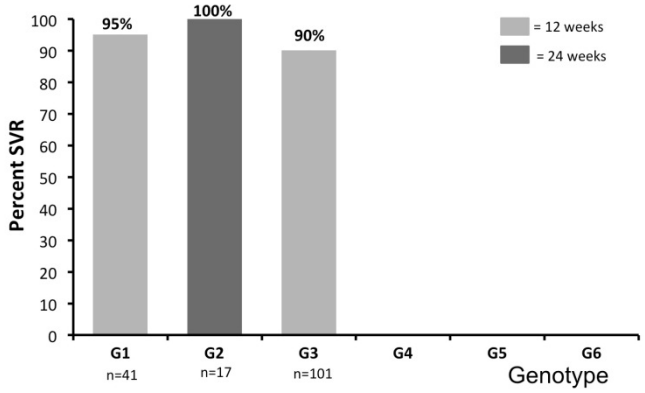
***Sofosbuvir + daclatasvir***

An especially promising combination, SOF + DCV, is a potentially pan-genotypic, once-daily regimen that was found to be highly effective, safe and tolerable in a Phase II trial. Available evidence indicates that this combination is likely to be pan-genotypic, safe and tolerable, simple to administer and take, and effective and durable.

In genotype 1, SVR exceeded 95%, including in people who were unsuccessfully treated with BOC- and TPV- based regimens (Figure 9). In treatment-naïve patients with genotype 1, SOF + DCV was found to be as effective at 12 weeks as at 24 weeks *[123]*. High SVR rates were also found in individuals with genotypes 2 and 3. Development of this promising combination was delayed by the refusal of Gilead to continue a clinical collaboration with Bristol-Myers Squibb; nevertheless, currently, three Phase III trials are ongoing.

Meanwhile the European Product Authorization Report for DCV refers to its use in combination with SOF in genotypes 1 and 4, and combination with SOF + RBV in genotype 3 *[124]*.

**Figure 9. Sofosbuvir + daclatasvir: SVR after 12 or 24 weeks**




*Sources* of data: G1-G3: A1444040 trial; G3: ALLY-3
Notes: G = genotype. No bar means no data (not "zero efficacy").

Though there is currently no evidence regarding the efficacy of this combination in coinfected patients, results from clinical trials are expected in early 2015. It is expected that SOF + DCV will be equally effective in coinfected patients, since SVR rates normally do not differ by HIV status.

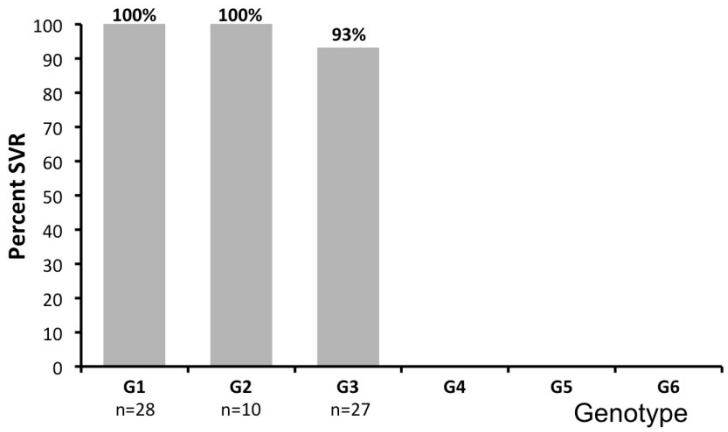
Results from a Phase II trial indicate that side-effects associated with SOF + DCV are mild-to-moderate, most frequently involving headache, nausea and fatigue *[123]*. Both drugs can be used without dose adjustment in patients with mild-to-moderate renal impairment and in all stages of hepatic impairment. SOF + DCV also may be used with most ARVs, although dose adjustments are needed when patients are receiving efavirenz, Stribild® or ritonavir-boosted atazanavir *[125]*. SOF + DCV may be co-administered with methadone or buprenorphine, although rifampicin, rifabutin and rifapentine are contraindicated for this regimen. SOF + DCV may be taken with or without food and stored at room temperature (below 30˚C).

***Sofosbuvir + GS-5816***

Gilead is developing an NS5A inhibitor, GS-5816, co-formulated with SOF. This combination is intended as a once-daily, pan-genotypic combination. Only preliminary data are available regarding SOF + GS-5816, as an FDC of this combination has entered Phase III trials, with results expected by the end of 2015. Trial data are available only in mono-infected patients, and no trials of this regimen are currently known to be planned for HIV/HCV coinfected patients.

Preliminary data of SOF + GS-5816 are promising. In a Phase II dose-ranging trial in 154 HIV-negative, HCV treatment-naïve, non-cirrhotic study participants with HCV genotypes 1, 2, 3, 4 and 6 (and a single patient with genotype 5), 100% of participants with genotypes 1, 2, 5 and 6 were cured. SVR was 93% and 96% in genotypes 3 and 4, respectively (Figure 10) *[126]*.

**Figure 10. Sofosbuvir + GS-5816 (100mg): SVR after 12 weeks**

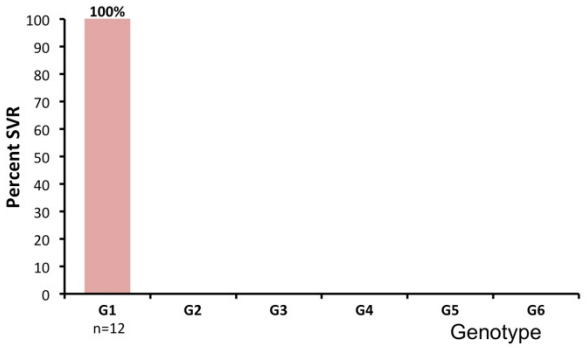



*Sources* of data: G1-3 Tran et al. *[127];* G3: ELECTRON-II; G4-G6 results: n<10
Notes: G = genotype. No bar means no data (not "zero efficacy").

***Other studies involving SOF***

Achillion's nucleotide polymerase inhibitor, ACH-3422, is in Phase I. A small "proxy" study of ACH-3422 + SOF (used as a placeholder for the company's own nucleoside/nucleotide polymerase inhibitor in early development) in 12 patients with genotype 1 found that all were cured (Figure 11) *[128]*. Other companies also may have conducted small-scale studies in which SOF was used as a proxy.

**Figure 11. Sofosbuvir + ACH-3102: SVR after 8 weeks**




*Source* of data: Gane et al. [128].
Notes: G = genotype. No bar means no data (not "zero efficacy").

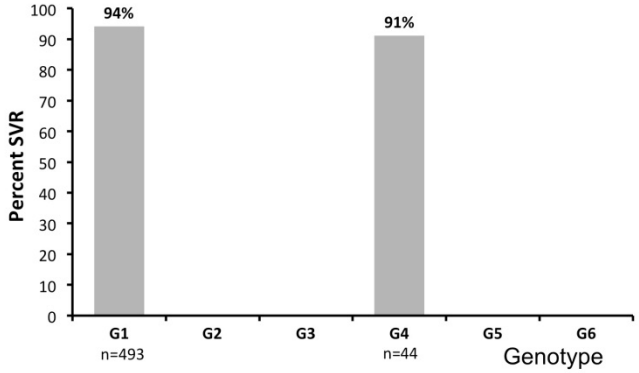
**c. Non-sofosbuvir combinations**

***Ombitasvir/paritaprevir/ritonavir + dasabuvir***

In late 2014, Swiss Medic, USFDA and Health Canada approved the combination of the FDC ombitasvir/paritaprevir/ritonavir (EU brand name Viekirax®) with dasabuvir (EU brand name Exviera®) for the treatment of HCV genotype 1, with or without RBV. The combination, produced by AbbVie, is also known as "3D". 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 12), this regimen is fairly complex; it comprises three tablets in the morning and another in the evening. People with genotype 1a are required to add twice-daily RBV, and 24 weeks of treatment are required for some patients (cirrhotic, treatment-experienced with genotype 1a).

**Figure 12. Ombitasvir/paritaprevir/ritonavir + dasabuvir: SVR after 12 weeks**




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

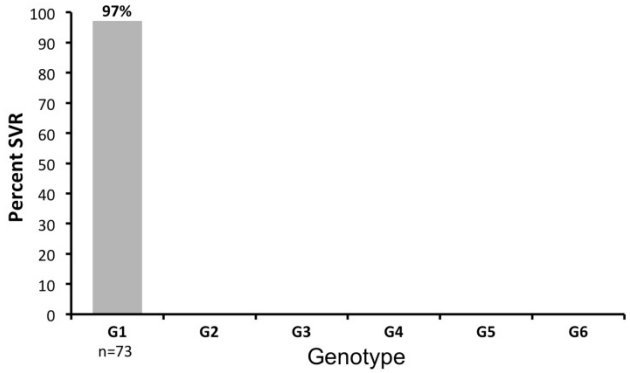
This combination is generally well-tolerated *[129]*. Although 89% of participants in the SAPPHIRE-I trial experienced at least one adverse event, side-effects tended to be mild-to-moderate. Headache and fatigue were the most commonly reported side-effects among trial participants. However, as RBV is independently associated with side-effects, its use with "3D" can cause or worsen the combination's side-effect profile. In addition, there are many drug – drug interactions.

***MK-5712/MK-8742***

MK-5712 and MK-8742 have been formulated together in a once-daily FDC that combines a protease inhibitor and an NS5A inhibitor. Currently in Phase III, this combination is being evaluated without RBV in genotypes 1, 4 and 6 and in combination with SOF in genotypes 1 and 3. A separate 300-person trial is planned to investigate the combination's safety and effectiveness in patients receiving opioid substitution therapy.

Among persons with genotype 1, cure rates exceeding 90% have been found for both mono-infected and coinfected patients (Figure 13). However, due to drug – drug interactions, the MK-8742/MK-5172 combination can be used only with certain ARV regimens [54].

**Figure 13. MK-8742 + MK-5172: SVR after 12 weeks**




*Source* of data: G1: C-WORTHY (AASLD 2014)
Note: G = genotype. No bar means no data (not "zero efficacy").

In 2014, Merck, the maker of this combination, also purchased Idenix, acquiring two nucleotides, IDX21459 (Phase I) and IDX21437 (early Phase II) as well as multiple patents on drugs in this class. Combined with early promising results from MK-8742/MK-5172, Merck's move opens up the possibility for a NS5A/nucleotide combination, or potentially for a three-class, short-course regimen for genotype 1.

***Other combinations***

AbbVie's combination of ABT-493/ABT-530 pairs a protease inhibitor and an NS5A inhibitor. This second-generation combination, which may have pan-genotypic qualities, has entered Phase II.

Other combinations, such as asunaprevir/DCV and asunaprevir/BMS-791325/DCV are being studied for use in genotype 1.

# 6. Market landscape

As the technology landscape demonstrates, the world is on the cusp of having available for use a pan-genotypic, safe, tolerable, highly effective, simple and user-friendly treatment to cure HCV infection. Available data suggest that the treatments that meet these criteria will be useful for both HIV/HCV coinfected and mono-infected patients and for patients with cirrhosis as well as those at an earlier stage of HCV disease.

However, one aspect of the target product profile remains unsatisfied, namely affordability. At present, new treatments are vastly too expensive to permit rapid scale-up in resource-limited settings. Indeed, these new treatments are so costly that many high-income countries are struggling to pay for them.

This section describes the market for the breakthrough HCV medicines that have the potential to reduce radically the health burden associated with HCV infection. The section examines both challenges associated with ensuring a robust supply of HCV drugs as well as market forces affecting the procurement and distribution of these medicines.

The market for DAAs is new in all parts of the world and virtually non-existent at present in low- and middle-income countries. As most of the DAAs discussed above have either only recently been approved or are yet to receive regulatory approval, market information is available only for the limited number of countries where the new DAAs have already been launched. Although this section demonstrates that the broad outlines of the market challenge posed by new DAAs are now apparent, many of the details will become clear only in the coming months and years.

## Market for existing products

This section describes market dynamics associated with the DAAs, as well as issues related to the potential production of generic DAAs. As the emerging backbone of HCV treatment, SOF is the primary focus of this section, which also provides information on the supply of other DAAs where it is available.

### 1. Regulatory approval

BOC and TPV were approved by the USFDA in May 2011. SIM and SOF received their first marketing approval by a stringent regulatory authority in the second half of 2013. Seven further DAAs were approved for use in at least one country in 2014. Table 7 provides an overview of the registration dates of those nine new DAAs as of 31 December 2014, inasfar as data are available.

As of 9 December 2014, SOF was registered in one middle-income country (Egypt). Its registration was pending in two low-income countries, six lower-middle-income countries and four upper-middle-income countries, while Gilead was planning to file for registration in another 16 low- and middle-income countries (see Annex 4).

### Table 7. Overview of registration date of new DAAs (as of 31 December 2014)

| | simeprevir | sofosbuvir | asunaprevir | daclatasvir | vaniprevir | ledipasvir (FDC with sofosbuvir) | dasabuvir | ombitasvir (FDC with paritaprevir + ritonavir | paritaprevir (FDC with ombitasvir + ritonavir) |
|---|---|---|---|---|---|---|---|---|---|
| **Australia** | 18 July 2014 | 30 June 2014 | -- | -- | -- | -- | -- | -- | -- |
| **Canada** | 18 Nov 2013 | 13 Dec 2013 | -- | -- | -- | 15 Oct 2014 | 22 Dec 2014 | 22 Dec 2014 | 22 Dec 2014 |
| **Egypt** | | July 2014 | | | -- | | | | |
| **European Union** | 14 May 2014 | 16 Jan 2014 | -- | 22 Aug 2014 | -- | 17 Nov 2014 | -- | -- | -- |
| **Japan** | 27 Sep 2013 | -- | 4 July 2014 | 4 July 2014 | 26 Sep 2014 | -- | -- | -- | -- |
| **Mexico** | July 2014 | -- | | | -- | | | | |
| **New Zealand** | -- | 20 Mar 2014 | -- | -- | -- | 6 Nov 2014 | -- | -- | -- |
| **Russia** | Mar 2014 | | | | -- | | | | |
| **Switzerland** | -- | 18 Mar 2014 | -- | -- | -- | 16 Dec 2014 | 25 Nov 2014 | 25 Nov 2014 | 25 Nov 2014 |
| **USA** | 22 Nov 2013 | 6 Dec 2013 | -- | -- | -- | 10 Oct 2014 | 19 Dec 2014 | 19 Dec 2014 | 19 Dec 2014 |

Notes: -- means the product is not registered as of 31 December 2014. A blank means no information available. Date of first worldwide registration is underlined. According to some reports, sofosbuvir was registered in Pakistan in September 2014; however, other reports contradict this (see also note in Annex 4). * Merck has announced that vaniprevir will be made available only in Japan.

## 2. Sales to date

The two DAAs with the largest sales as of 31 October 2014 – SOF and SIM – are manufactured and sold by Gilead Sciences and Janssen respectively. Both are "blockbuster" medicines,[11] and SOF is likely to become a record-breaking new drug in terms of sales *[131]*.

As no generic alternatives currently exist for any of the new DAAs, sales to date have involved purchases from originator manufacturers. As Tables 8 and 9 indicate, the sales figures of both SOF and SIM have been impressive since their launch in late 2014. In the first 13 months following initial regulatory approval, SOF generated nearly US$ 10.5 billion in sales, while over US $2 billion has been spent on procurement of SIM between its launch in November 2013 and 31 December 2014 (Figure 14). [12]

### Table 8. Global sofosbuvir sales (US$ thousands), by quarter-year (Q)

| | Q4 2013 | Q1 2014 | Q2 3014 | Q3 2014 | Q4 2014 | Total |
|---|---|---|---|---|---|---|
| **USA** | 136 364 | 2 097 791 | 3 031 507 | 2 199 519 | 1 178 000 | **8 643 181** |
| **Europe** | 3071 | 163 691 | 400 218 | 523 455 | 459 000 | **1 549 435** |
| **Rest of world** | -- | 12 867 | 48 601 | 73 119 | 95 000 | **229 587** |
| **Total** | **139 435** | **2 274 349** | **3 480 326** | **2 796 093** | **1 732 000** | **10 422 203** |

*Source:* Gilead.

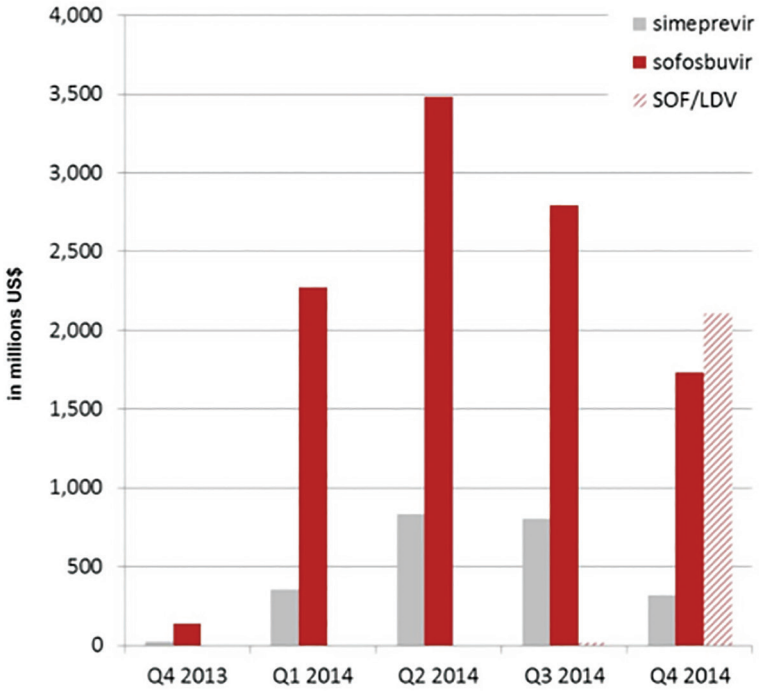
11 "A 'blockbuster medicine' is defined as being one that achieves annual global revenues of over US$ 1 billion." [130].
12 Though approved in September, SIM was launched in Japan only on 6 December 2013.

**Table 9. Global simeprevir sales (in US$ thousands), by quarter-year (Q)**

| | Q4 2013 | Q1 2014 | Q2 3014 | Q3 2014 | Q4 2014 | Total |
|---|---|---|---|---|---|---|
| **USA** | 13 000 | 291 000 | 725 000 | 671 000 | 256 000 | **1 943 000** |
| **Rest of world** | 10 000 | 63 000 | 109 100 | 133 900 | 65 000 | **371 000** |
| **Total** | **23 000** | **354 000** | **834 100** | **804 900** | **321 000** | **2 314 000** |

*Source:* Johnson & Johnson and Medivir.

**Figure 14. Global sales of sofosbuvir, simeprevir and SOF/LDV, Q4 2013–Q4 2014**




*Source* of data: Gilead, Johnson & Johnson and Medivir.

Two other DAAs were launched in the third quarter of 2014. Asunaprevir was launched in Japan in September 2014. DCV was launched in Germany in August 2014 and in certain other European countries and Japan in September 2014. Each of these products achieved sales of more than US$ 10 million during the quarter in which they were launched. The same applies to AbVie's "3D" combination, launched in the last quarter of 2014 (Table 10). "Early access" sales of Harvoni® (FDC of SOF and LDV) in the third quarter of 2014 – i.e. before its launch in October 2014 – equally surpassed US$ 10 million. Global sales of Harvoni® surpassed US$ 2 billion in the quarter in which it was launched (the last quarter of 2014), mainly due to its US sales (94% of Harvoni® sales in 2014 took place in the USA).

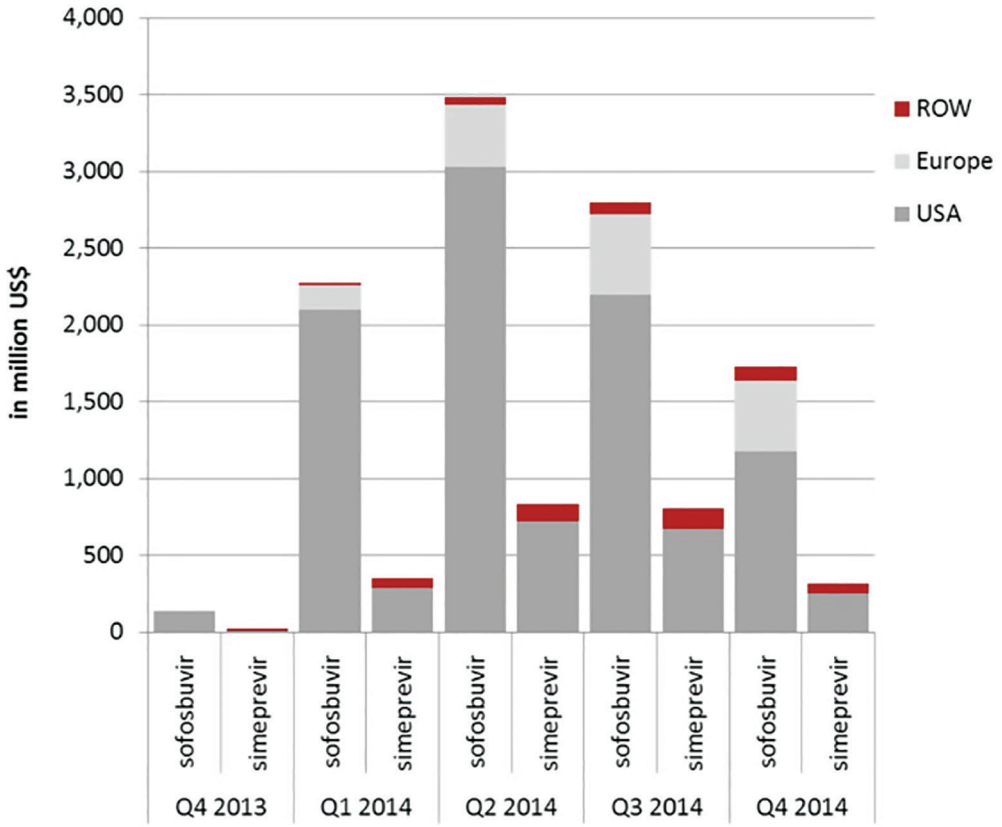
**Table 10. Sales of other DAAs (in US$ thousands), Q3–Q4 2014**

| Product | Region | Q3 2014 | Q4 2014 | Total |
|---|---|---|---|---|
| asunaprevir | Japan | 11 000 | 44 000 | **55 000** |
| daclatasvir | Europe and Japan | 38 000 | 163 000 | **201 000** |
| Harvoni® (SOF/LDV) | Q3: Europe (early access sales)<br>Q4: Europe, USA and ROW | 19 966 | 2 107 000 | **2 126 966** |
| Viekira | USA | -- | 48 000 | **48 000** |

*Sources:* AbbVie, Bristol-Myers Squibb and Gilead.

However, resource-rich settings account for nearly all sales of the new DAAs, with minimal penetration in low- and middle-income countries. In the first 13 months of SOF marketing, the USA and Europe accounted for more than 97% of worldwide SOF sales (Figure 15).

**Figure 15. Global sales of simeprevir and sofosbuvir by geographical region (Q4 2013–Q4 2014)**



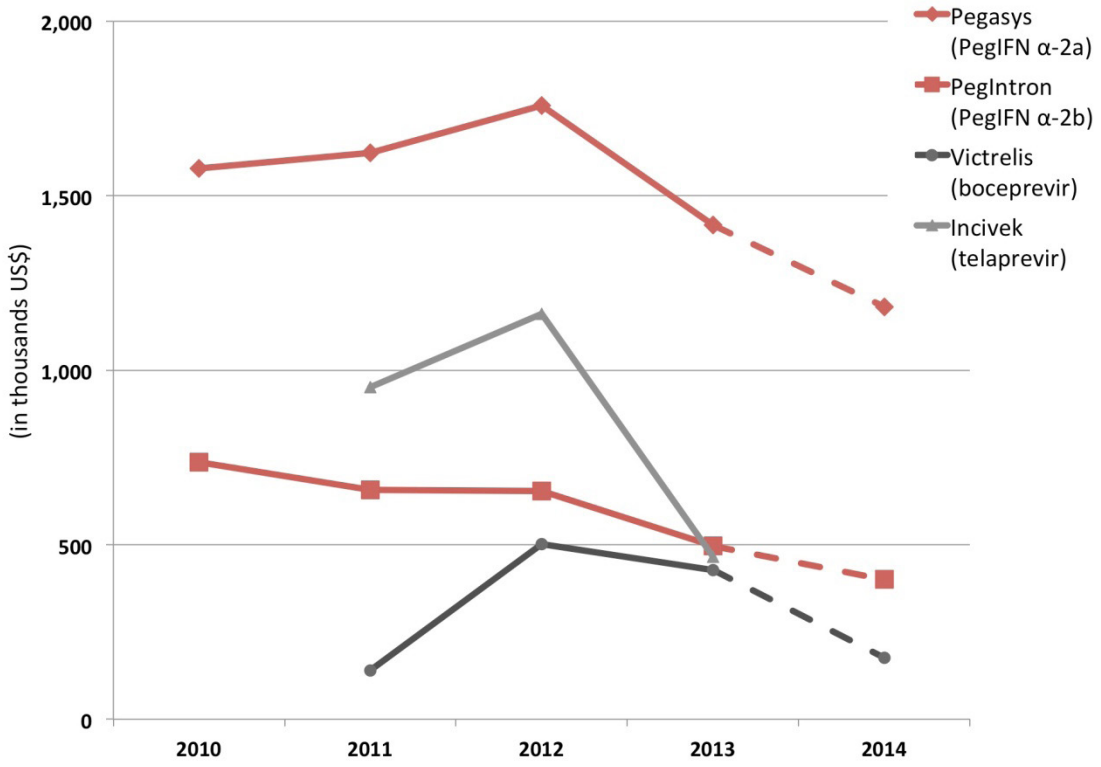

*Source* of data: Gilead, Johnson & Johnson and Medivir.
Note: ROW = rest of world.

The emergence of highly effective DAAs has resulted in a substantial expansion of the global market for HCV medicines. Together, SOF and SIM accounted for more than US$10 billion in sales during the first nine months of 2014 – twice the total market value of HCV drugs in 2012, which amounted to around US$ 5 billion (Peg-IFN and RBV together represented US$3.5 billion in purchases in 2012, with BOC and TPV accounting for the remainder).[13] Predictably, the older HCV medicines have lost market share (Figure 16).

13 Merck, Roche and Vertex 10K reports.

Vertex announced in August 2014 that it would stop marketing TPV in the USA "in view of available alternative treatments and the diminishing market demand" *[85]*. Merck made a similar announcement regarding boceprevir in January 2015, citing "scientific advancement, changes in treatment practices, and the consequent reduction in the demand" as the reasons for its decision *[84]*.

**Figure 16. Global sales of Peg-IFN, boceprevir and telaprevir (2010–2014)**




*Sources:* Merck, Roche, Vertex.
Notes: Sales for 2014 have been estimated by extrapolating sales data for Q1–3, 2014 (where available).
Pegasys sales have been converted from CHF using average annual exchange rates (OANDA).
Boceprevir and telaprevir received marketing approval in May 2011.

## 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 sells to the general market for US$ 1000 a pill, or US$ 84 000 for 12 weeks of treatment (Table 11). SIM sells for a somewhat lower, but still extremely high, price. The prices of these individual drugs actually understate total costs for state-of-the-art HCV treatment, as both SOF and SIM are intended to be used in combination with additional drugs. In the USA, the price for a 12-week course of Harvoni® (SOF + LDV) is US$ 94 500.

In high-income countries where the public sector plays a more pronounced role in health-care financing than the USA, lower – although still substantial – prices have been negotiated. France has reportedly negotiated the lowest price for SOF in Europe, at US$ 51 400 for 12 weeks of treatment *[132]*. Spain has also negotiated a price for SIM that is roughly half of the price charged in the USA *[133]*. Notable discounts off the USA prices were also negotiated for both SOF and SIM by the United Kingdom *[134]*, while Canada and Switzerland *[135]* have obtained a comparable deal for SOF *[136]*. In the USA, the Veterans Administration, which is responsible for the financing and delivery of health care for people who have served in the USA military, has also negotiated prices for SOF and SIM that are more than 40% lower than the commercial price *[137]*.

**Table 11. Prices for 12 weeks of treatment**

| | SIM | | SOF | | SOF/LDV | | Viekira Pak® |
|---|---|---|---|---|---|---|---|
| | Original currency | US$ | Original currency | US$ | Original currency | US$ | US$ |
| **USA** | | $ 66 360<br>$ 31 500** | | **$ 84 000**<br>**$ 45 612****| | $ 94 500<br>$ 69 636** | $ 83 319 |
| **Canada** | | | **$ 55 000** | ± $ 49 730 | | | |
| **Egypt** | | | | $ 900 | | | |
| **France** | | | **€ 56 000**<br>**€ 41 000*** | ± $ 71 630<br>± $ 52 440* | **€ 48 000** | ± $ 61 400 | |
| **Japan** | | $ 11 244 | | | | | |
| **Spain** | **€ 25 000*** | ± $31 980* | | | | | |
| **Switzerland** | | | **CHF 57,600** | ± $60 390 | | | |
| **United Kingdom** | **£ 22 398** | ± $ 36 560 | **£ 34 983** | ± $ 57 100 | | | |

* Negotiated for government reimbursement scheme. ** Lowest reported price negotiated by the USA Department of Veterans. Conversions to US$ based on average exchange rates for Quarters 1–3, 2014 (OANDA).

Even with these negotiated prices, costs associated with SOF remain considerable. According to one international NGO coalition, treating all HCV-infected individuals in France who have fibrosis would cost more than the budget of the Parisian public hospital system *[138]*. Cost concerns have prompted national authorities in some high-income countries to ration new DAAs, prioritizing individuals with advanced or symptomatic infection *[138]*.

In the USA and other high-income countries, Gilead has received considerable criticism for its pricing of SOF. Health advocates and patient groups have decried the high price of SOF *[139]*, and administrators of public sector health programmes in the USA (e.g., Medicare, Medicaid) have warned that the price structure for SOF threatens to place severe financial strains on their programmes and have placed restrictions on access *[140]*. Some high-income countries (e.g., Spain) are reportedly refusing to cover SOF with public sector funds due to its high price. Business-friendly publications, such as *Forbes* in the USA, have stated that Gilead cannot justify the price it is charging for SOF in high-income countries *[141]*.

There were hopes that the approval of competing DAA regimens would result in price competition and thus would contribute to lower prices for HCV treatment generally. However, in the USA, the commercial price for Viekira Pak® is roughly equivalent to the price for SOF – though there are signs that some competition may emerge through the negotiation of exclusive deals for "preferred" regimens at undisclosed "significantly lower" prices by large buyers such as pharmacy benefit managers and health insurers *[142, 143]*.

In May 2014, Egypt, the country with the highest HCV prevalence, and Gilead concluded a deal whereby the country will be able to purchase a 12 weeks' course of SOF for US$ 900 – a 99% discount on the commercial price in the USA *[144]*. In rolling out SOF access, Egypt has prioritized people with severe disease and those who are unable to pay by themselves *[145]*. Aid groups are reportedly able to purchase SOF for the same US$ 900 price for use in other resource-limited countries. There are also reports that the price of US$ 900 is being offered to some other countries, such as Mongolia *[146]*, although as of December 2014 no country other than Egypt is known to have reached agreement with Gilead on public-sector pricing for SOF.

## 4. Patents and licences

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 keeps the price high.

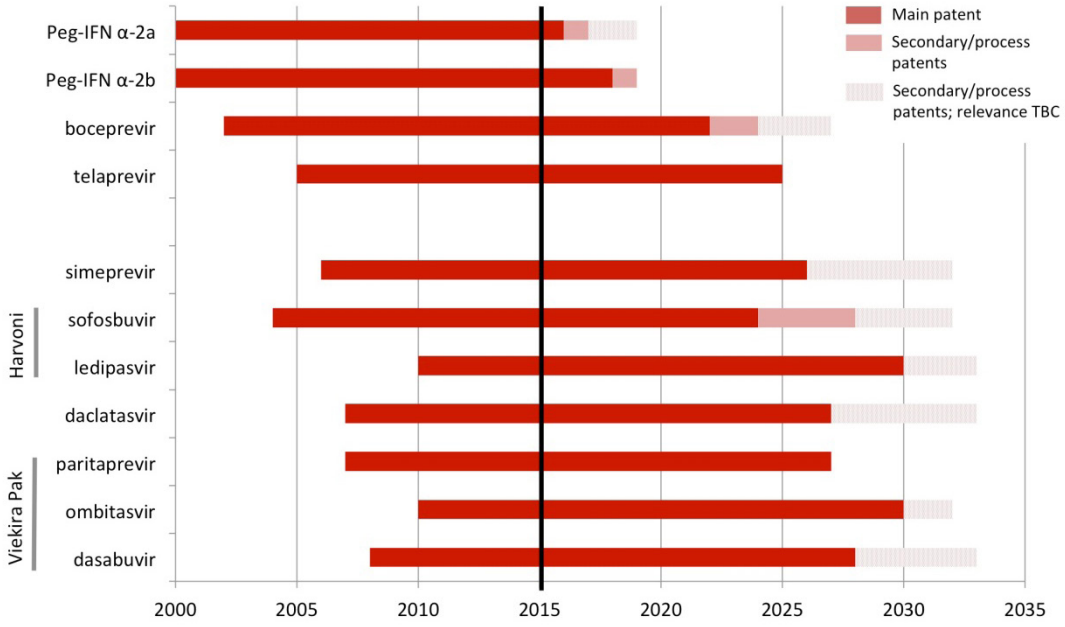
Medicines are usually subject to multiple patents which fall in several broad categories, notably:

- *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.

Patents on RBV have expired and generic versions are available. However, most other HCV medicines are still patented. Where granted, patents on Peg-IFN may last until 2019 *[147]*. Alternative (non-originator) versions of Peg-IFN are available in some countries *[148]*.

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 5. 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 *[38–44]*.

It has however been suggested that the patents for SOF are weak *[149]*. Not-for-profit organizations and generic companies have questioned the patentability of SOF and have filed pre-grant oppositions to patent applications for SOF in India *[150–152]*.

In February 2014, the patent office in Egypt reportedly rejected a patent application for SOF for lack of novelty and lack of inventiveness (though the decision is still believed to be under appeal). In January 2015, the Patent Office of India also rejected a (different) patent application on SOF. This decision, which relates to one of the key patents on SOF, is important and may help increase opportunities for generic manufacturing in India; however its implications are likely to be limited[14] as multiple other patent applications (including some that are relevant to the production of generic versions of SOF) are still pending.

Meanwhile, Gilead, in September 2014, signed voluntary licences for SOF and LDV with seven major generic producers in India. As licence-holders, these companies have the right to manufacture generic versions of SOF and LDV. The licence, which has been made public, allows these companies to supply generic versions to 91 low- and middle-income countries, including all low-income countries and all but one least-developed country. The licence also includes 37 of 50 (74%) lower-middle-income countries and 17 of 55 (30%) upper-middle-income countries – which is about half (51%) of all middle-income countries. However, it excludes countries such as China, which has the largest number of people with HCV, and Ukraine (see Annex 6 for the list of countries that are included in the licence). On 26 January 2015, Gilead announced that its investigational compound GS-5816 will be included in these voluntary licences *[153]*.

In November 2014, Bristol-Myers Squibb likewise announced its intention to issue voluntary licences for DCV. To date, few details are available on the planned DCV licences and, as far as is known, none has been signed. The company did, however, announce the names of the 90 countries that would be covered by the licence; they include all low-income countries and least-developed countries, as well as the middle-income countries covered by the Gilead licences, with the notable exception of Egypt (Annex 6).

***Voluntary licences on sofosbuvir***

Licensing schemes offer a potentially important avenue for expanding access to new medicines for patients in resource-limited countries. Licenses 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.

As noted, Gilead has issued voluntary licences. These voluntary licences include a number of middle-income countries with significant numbers of people with HCV, such as Egypt and Indonesia. This may create sufficient demand to enable economies of scale.

The licence covers SOF, LDV and SOF/LDV, and allows for the development of FDCs of SOF and/or LDV with other HCV medicines. GS-5816 has been included in the licences in January 2015. Another positive feature of these licences is that they allow generic companies to supply to countries that are not included in the licence in case 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 12 summarizes the options and questions regarding the supply to the "excluded" middle-income countries such as Brazil (home to an estimated 2.6 million people with HCV), Thailand (1.5 million) and Morocco (625 000) *[138]* by Indian generic companies that hold a licence.

14 Moreover, Gilead reportedly is appealing the rejection *[154–156]*.

**Table 12. Overview of options for supply of generics by Gilead licence-holders to countries excluded from the licence**

| Patent status in India | Patent status in importing country (not included in licence): Patent(s) granted | Patent(s) pending | Patent(s) rejected but appealed | No patents (including final rejection) |
|---|---|---|---|---|
| **Patent(s) granted** | Yes if CL issued in importing country or CL for export in India | Yes if CL for export issued in India | Yes if CL for export issued in India | Yes if CL for export issued in India |
| **Patent(s) pending** | Yes if CL issued in importing country | Can CL be issued on non-granted patent? Is there no "reasonable possibility" for Gilead to obtain a patent? | Can CL be issued on non-granted patent? Is there no "reasonable possibility" for Gilead to obtain a patent? | Can CL be issued on non-granted patent? Is there no "reasonable possibility" for Gilead to obtain a patent? |
| **Patent(s) rejected but appealed** | Yes if CL issued in importing country | Can CL be issued on non-granted patent? Is there no "reasonable possibility" for Gilead to obtain a patent? | Can CL be issued on non-granted patent? Is there no "reasonable possibility" for Gilead to obtain a patent? | Can CL be issued on non-granted patent? Is there no "reasonable possibility" for Gilead to obtain a patent? |
| **No patents (incl final rejection)** | Yes if CL issued in importing country | Can CL be issued on non-granted patent? Is there no "reasonable possibility" for Gilead to obtain a patent? | Can CL be issued on non-granted patent? Is there no "reasonable possibility" for Gilead to obtain a patent? | Yes |

"Yes" means generic companies that hold a licence for SOF, LDV, GS-5816 from Gilead will be able to supply. "CL" means compulsory licence.

= 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 in these cases.

The countries included in the licences (see Annex 6) will be able to buy generic versions of SOF, LDV and GS-5816 once these become available from the licence holders, regardless of whether or not patents are granted in these countries. If there are no patents, these countries may also buy from other generic manufacturers, if any.

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 5) – a compulsory licence would have to be issued on those pending patents in the concerned country and/or in India. However, it is not clear whether national patent laws provide for the granting of compulsory licences on pending patents.

In case 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 *[170]* and several other patent applications are currently pending there *[44, 181]*, 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 a compulsory licence has been issued, countries outside the licence could also buy generics from other (non-licence-holding) manufacturers, if any. Or countries could opt for local production, provided they can find a source of API[15] or are able to produce the API locally.

15 The licence imposes conditions on API manufacturers that are similar to the conditions on finished products. In addition, API produced under the licence may be supplied only to generic manufacturers in India that hold a license.

***Generics under development***

Licensed generic manufacturers in India are currently working to develop generic versions of SOF for marketing in resource-limited settings. Industry representatives indicate that generic SOF is likely to be available by the end of 2015 or in 2016.[16]

Pharco and other pharmaceutical companies in Egypt are also developing generic versions of SOF. They do not need a licence as the key patent for SOF has been rejected in Egypt.[17] In November 2014, Pharco signed a licence for a pipeline NS5A inhibitor, PPI-668 *[157]*.

## 5. Production costs

Reportedly, SOF and other DAAs are not especially costly to produce. Researchers from South Africa, United Kingdom and the USA used available data to estimate costs associated with the production of HCV treatment for 1 – 5 million patients per year with various DAA combinations *[158]*. Beginning by estimating the costs of production of the API for each DAA, the team added 25% as a profit mark-up and 40% as the estimated cost of producing the finished pharmaceutical product. Using this approach, the team estimated the minimum production costs for selected DAAs (Table 13).

**Table 13. Estimated production cost of selected DAAs** *[158, 159]*

| | Estimated cost per gram (US$) | Estimated cost for 12 weeks of treatment (US$) |
|---|---|---|
| daclatasvir | 4.00 | 20 |
| ledipasvir | 12.25 | 93 |
| simeprevir | 10–21 | 130–270 |
| sofosbuvir | 3.00 | 101 |
| **Pipeline products** | | |
| MK-8742 | 10.50 | 44 |
| MK-5172 | 8.75 | 74 |

On the basis of these estimates, the costs for 12 weeks of treatment with selected combinations of DAAs were estimated, as follows:

- US$ 149 per person for SOF + RBV;
- US$ 193 for SOF + LDV;
- US$ 121 per person for SOF + DCV; and
- US$ 118 for MK-8742 + MK-5172 *[158, 159]*

It should be noted that these are estimates of minimum costs and that they presume sufficient volumes.

Meanwhile, preliminary information obtained from generic producers and API manufacturers indicates their interest in the HCV market. It is too early to obtain a firm market entry price for generic products, but most producers have indicated they would be able to offer SOF for less than US$ 900 for 12 weeks of treatment (Gilead's price for SOF in Egypt). Some experts on API production cautiously predict a market entry price for the finished formulation of US$ 500 per treatment course. This price, and possible subsequent further decreases, will critically depend on volumes.[18]

16 Remarks by Soni A, Mylan Inc. at Global Challenges Seminar – Innovation and Access to Medicines: A Case Study for HIV/AIDS and Hepatitis C. Geneva: World Intellectual Property Organization; 5 December 2014.

17 However, as mentioned above, it is believed that Gilead's appeal is still pending.

18 The order of magnitude would be around 10 metric tonnes of API (i.e. 25 million doses, or 12 weeks of treatment for 300 000 people). Competition among multiple suppliers is assumed, as is a sustainable and predictable demand.

## Market forces

As the record-breaking early sales of SOF illustrate, there is robust demand for DAAs among people infected with HCV in high-income countries. Similar demand is likely in some resource-limited settings; in the first several weeks in which patients were able to apply to receive SOF in public sector settings in Egypt, 100 000 individuals came forward seeking the drug *[145]*. As the previous discussion indicates, generic DAAs are likely to become available in the foreseeable future, potentially offering opportunities to roll out these breakthrough therapies in low- and middle-income countries.

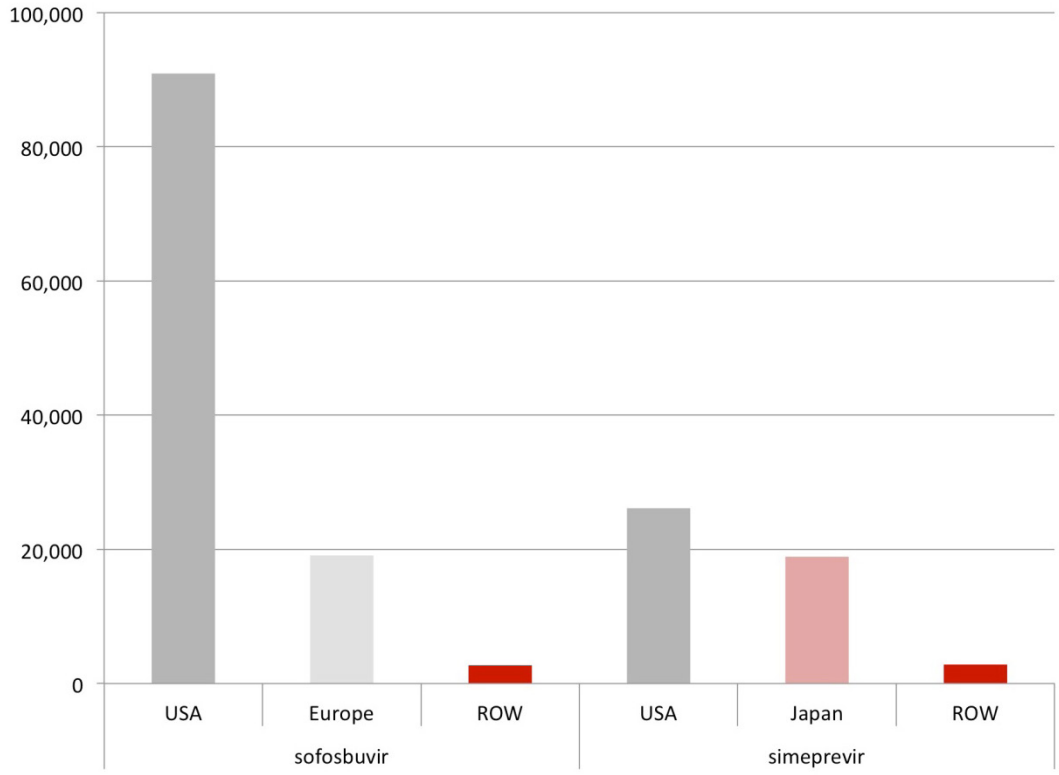
However, if current conditions persist, the needed volume of DAAs is unlikely to materialize in resource-limited settings. Following a brief review of the very low market penetration of DAAs in low- and middle-income countries to date, this section explores the various factors that could constrain the development of robust demand for DAAs in these countries.

### 1. Access to date

On the basis of the sales data, prices and registration data above, it is possible to estimate that, worldwide, around 48 000 people have been treated with SIM and around 113 000 have had access to SOF between the launch of these products in the last quarter of 2013 and 30 September 2014. The geographical distribution of people who have been treated with SOF or SIM (see estimates in Figure 18) show that there has been minimal access to these drugs outside Europe, Japan, and the USA.

It may be noted that SOF sales in the rest of the world (indicated by "ROW" in Figure 18) appear to refer exclusively to high-income countries; SOF was registered in Egypt and possibly Pakistan before the end of Quarter 3 (Table 7) but actual distribution began in mid-October in Egypt *[160]* and reportedly had not yet started in Pakistan as of November 2014 *[161–162]*.

**Figure 18. Estimated number of people treated by region (Q4 2013–Q3 2014)**




See Annex 7 for sources and methodology used to prepare these estimates.

## 2. Funding availability for procurement of DAAs

In low- and middle-income countries, the primary purchasers of DAAs are likely to be national governments and international donors if these treatments are to be rolled out. The private sector may also play a role in the financing and delivery of DAAs in some countries, although this role is likely to be limited unless treatment becomes more affordable. To generate volumes sufficient to enable generic companies to achieve economies of scale and lower prices for DAAs, robust funding for procurement of DAAs will be required.

The potential interest of national governments in purchasing DAAs is unclear. Egypt has already purchased enough SOF doses to treat 70 000 people *[145],* which represents slightly over 1% of the number of Egyptians with chronic HCV *[163].* Other countries believed to be interested in providing HCV treatment include, for example, Brazil, Mongolia and Viet Nam.

In the case of HIV, many national governments have sharply ramped up domestic public-sector spending for the procurement of ARVs, with domestic sources accounting for a majority of global HIV spending in 2013 *[164].* While ART for HIV infection may be the closest analogy to the challenge of scaling up HCV treatment, the analogy is imperfect. On the one hand, the annual costs of treating a case of HIV infection (estimated as US$ 338 in 2013 *[165]* is less than the cost of a 12-week HCV treatment course negotiated by Egypt. On the other hand, HIV treatment is lifelong whereas HCV treatment lasts for 12 weeks and results in a cure.

To date, international donors have offered limited support for HCV treatment, due in no small measure to the very high current prices for these medicines. As of November 2014, the Global Fund to Fight AIDS, Tuberculosis and Malaria had provided limited funding to support HCV treatment in Belarus, Georgia, the former Yugoslav Republic of Macedonia, Thailand and Ukraine, primarily for Peg-INF + RBV *[166].*

Bilateral funding for HCV treatment is believed to be limited or non-existent. The United States President's Emergency Plan for AIDS Relief (PEPFAR) issued technical guidance in 2013 prohibiting use of PEPFAR funding for HCV treatment with Peg-IFN + RBV, citing its complexity, toxicity and expense *[167].*

Obtaining sharply lower prices that are broadly applicable to low- and middle-income countries may be a prerequisite for robust donor engagement in this field. This risks creation of a vicious circle: generic companies may require large volumes in order to lower prices, while donors will need lower prices in order to commit sufficient funding to enable large-volume purchases.

## 3. Demand impediments

Even with sharply lower prices, uptake of DAAs will be limited by the fact that the majority of people with HCV do not know they are infected. In some European countries, where HCV treatments have long been available through well-established public-sector health delivery sites, a majority (perhaps as high as 90%) of people infected with HCV are undiagnosed *[163].* In low- and middle-income countries, where access to HCV treatment has been minimal, it is reasonable to assume that knowledge of HCV status is considerably lower. Moreover, while screening for HCV and staging (necessary to make treatment decisions) involves a simple antibody test, currently diagnosis of HCV involves a costly, complex, multi-step process that is not suitable for large-scale implementation in low- and middle-income countries.

Nevertheless, several developments may aid in simplifying and streamlining HCV diagnosis. First, the emergence of short (duration of < 12 weeks), safe and truly pan-genotypic DAA regimens would obviate the need for genotyping and reduce monitoring requirements. This would simplify the diagnostic paradigm for HCV and reduce its cost. Second, new diagnostic tools are being developed, including assays for use at or near the point-of-care *[168].* These have potential to make HCV diagnosis feasible in more health facilities. The use of platforms that allow for combined testing for HIV, HCV and hepatitis B virus can also expand access to HCV diagnosis without adding significant extra costs compared to testing for HIV alone.

## Box 1. Anti-diversion policy

Concerns have been expressed that proposed anti-diversion measures for lower-priced SOF supplied by the originator will impose unreasonable hardships on patients and health-care providers. Intended to prevent resale in high-income countries, the anti-diversion policy would require disclosure of the patient's name and proof of residence and citizenship. The patient's name and address will reportedly be embedded in a scanable code on each bottle of medicine, enabling Gilead to trace the bottle. Each patient must sign an agreement to return the empty bottle before another bottle may be dispensed. Dispensing is strictly limited to Gilead's approved distributors. Médecins Sans Frontières and others argue that these rules violate patient autonomy and privacy and conflict with the rules of medical ethics as set out in the Helsinki Declaration *[169]*.

Furthermore the voluntary licences for SOF, LDV and GS-5816 require the implementation by generic licence-holders of anti-diversion measures for both API and finished products. While not fully detailed in the licence, these measures may include efforts to ensure that the generic product is sold "directly to patients" *[170]*.

### 4. Other potential impediments to uptake

In addition to cost, patent barriers and lack of demand, other factors have the potential to impede the uptake of DAAs.

- *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 steps and measures that are prerequisites for expanding access.
- *Regulatory delays.* As new drugs emerge for the treatment of HCV, delays in national registration have the potential to slow the availability of these drugs to patients who urgently need them *[45]*. 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 the originator companies.
- *Treatment guidelines.* As noted, the standard of care for HCV treatment is in flux, with the likely emergence of several new drugs suggesting that the standard will continue to evolve. In such a rapidly changing context, normative bodies at the global and national levels may struggle to keep pace with the latest scientific evidence, potentially delaying the introduction of optimal regimens.
- *Human and health systems readiness.* 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 relying on integrating HCV treatment in existing programmes, such as those for HIV, additional infrastructure will be required.
- *Stigma and discrimination.* Some national governments may refrain from prioritizing HCV treatment due to the epidemic's concentration in marginalized and stigmatized populations – notably people who inject drugs and men who have sex with men. This phenomenon has already been observed in the HIV epidemic, as national governments have largely failed to allocate substantial domestic resources to treatment and prevention programmes for these key populations *[8]*. While 37% of all adults living with HIV globally received antiretroviral therapy in 2013, UNAIDS estimates that only 10% of people who inject drugs accessed HIV treatment *[8]*. To the extent that HIV treatment and prevention programmes have been implemented for key populations in low- and middle-income countries, these have typically resulted from external donor support. In the case of HCV treatment, however, no comparable donor initiative has yet emerged.

# 7. Market shortcomings

## Situation analysis – key issues

### No "perfect" DAA regimen yet

The ideal regimen for treatment of HCV in resource-limited settings has not yet been identified. Data on the efficacy of existing products or regimens for certain genotypes or in specific populations are not (yet) available, and some potentially promising compounds are still in development. Research to fill information gaps is ongoing. However, originator companies tend to focus on the development of combinations of products within their own portfolio, while combinations with competitors' products – even if promising – may not be studied or may progress at a slower pace. Gaps in information may therefore remain.

Nevertheless, the contours of the products and regimens that best fit the target product profile (pan-genotypic; safe and efficacious, including for patients with HIV/HCV coinfection or cirrhosis; duration of < 12 weeks that does not vary by genotype) are rapidly becoming clearer.

### A vicious circle of high prices and low volumes

Prices of the new DAAs are very high in high-income countries. Significantly lower prices have been announced for SOF for low-income countries and for a number of middle-income countries, but the lowest current price (US$ 900 for 12 weeks' treatment in Egypt) is still expensive.

The new DAAs have been approved and launched only recently, and – as far as is known – are widely patented. In the absence of competition, prices are high. Voluntary licences granted for SOF and LDV enable early onset of generic competition but do not include all middle-income countries. Generic manufacturers are currently developing their products and are expected to enter the market in late 2015 or 2016. To bring prices down to affordable levels, generic companies will need volumes, yet at this stage the demand for DAAs is limited in many low- and middle-income countries. The inclusion of only 50% of all middle-income countries in the voluntary licences may function as a cap on volumes for generic suppliers.

Though there are notable exceptions, many low-and middle-income countries have limited government funding for HCV treatment. Most donors traditionally provide little or no funds for HCV treatment, due, at least in part, to its high cost. Thus, there is a risk of a vicious circle: donors and governments need low prices in order to consider funding the procurement of significant volumes, while generic manufacturers need volumes to reduce prices to affordable levels.

### Potentially limited uptake

The complexity and cost of diagnosis, and the lack of point-of-care confirmatory tests, limit options for diagnosis of active HCV infection. HCV-infected persons may therefore not know their status or may not be aware of the promising options for cure, which may limit the uptake of the new DAAs in some settings. Patent barriers – even if only on one particular DAA – may also limit the uptake of the best combination(s) or the most suitable dosage form(s) of DAAs in future.

## Summary of shortcomings and their reasons

A series of specific shortcomings that relate to these key issues are outlined in the matrix in Table 14, along with the reasons why they exist.

## Table 14. Market shortcomings and the reasons for them

| Availability | |
|---|---|
| **Market shortcoming** | **Reasons** |
| Lack of an HCV treatment regimen that satisfies requirements of the target product profile | Lack of information on safety and efficacy in some genotypes and for some groups of patients<br>Awaiting results of ongoing clinical trials<br>Commercial focus on development of in-house regimens rather than collaborating with others to optimize regimens |

| Affordability | |
|---|---|
| **Market shortcoming** | **Reasons** |
| Extremely high commercial prices for originator products | Substantial commercial mark-ups on products that are relatively inexpensive to produce<br>Lack of generic competition due to patent barriers and/or the fact that generic companies are still developing or optimizing their production processes<br>Market power associated with ownership of breakthrough treatments that achieve cure rates for HCV in excess of 90% |
| Lowest price for SOF (US$ 900 in Egypt) is still substantially higher than actual costs of production | Use of USA price as benchmark for pricing in low- and middle-income countries<br>Lack of generic competition<br>Negotiation of price that is well above the estimated minimum production costs |
| Patent barriers limit the options for generic production and use in low- and middle income countries | Active effort by originators to widely patent new products<br>Exclusion of 50% of middle-income countries from existing voluntary licensing agreements since originator companies seek to obtain higher prices from upper-middle-income countries |
| Uncertainty regarding price of generic DAAs (once they become available) | Generic manufacturers are still developing their products and may price them as high as possible<br>Generic manufacturers will need large volumes to achieve economies of scale to be able to offer affordable prices; however, demand in low- and middle income countries is not yet clear |
| Uncertainty regarding procurement volumes for low- and middle-income countries | Lack of donor programmes for HCV treatment scale-up, due to:<br>■ Relatively recent emergence of DAAs<br>■ Perception (based on USA commercial price) that DAAs are unaffordable in resource-limited settings<br>■ Lack of pre-existing funding and advocacy infrastructure for HCV treatment (e.g. HCV is not one of the three priority infectious diseases)<br>■ Perception that HCV is primarily a problem of middle-income countries<br>Uncertain national commitment to purchase HCV medicines, due to:<br>■ Relatively recent emergence of DAAs<br>■ Lack of national budget lines for HCV treatment in many countries<br>■ Perceptions (based on USA commercial price) that DAAs are unaffordable in resource-limited settings<br>■ Resistance to funding of HCV treatment due to stigmatization of heavily affected populations<br>■ Competing priorities |

| Delivery | |
|---|---|
| **Market shortcoming** | **Reasons** |
| New DAAs are not yet on the market in the majority of low- and middle-income countries | Originator companies register and launch their product(s) first in selected high-income countries; companies are just beginning to register their new medicines in low- and middle-income countries |
| Possible delays associated with regulatory approval processes | Weak or overburdened regulatory systems in a number of low- and middle-income countries<br>Still insufficient harmonization of regulatory schemes<br>Requirement for in-country clinical trials in some countries |
| Potential delays in uptake of normative guidance at country level | Rapid evolution of standard of care<br>Time and effort involved in development of new guidelines<br>Time and effort involved in translation of global guidance into national treatment guidelines |
| Inadequate health systems capacity | Shortages of health workers<br>Lack of capacity and guidance on HCV diagnosis<br>Lack of health workers trained in HCV treatment delivery, especially DAAs<br>Weak commodity procurement and supply management systems<br>Physical and systems infrastructure requirements associated with rapid scale-up of HCV treatment |

| Acceptability/adaptability | |
|---|---|
| **Market shortcoming** | **Reasons** |
| Lack of access to diagnosis which in turn limits demand for drugs | HCV diagnosis is complex and expensive<br>Capacity for diagnosis is often limited to one or a few reference laboratories<br>Lack of recognition of HCV risks by many people |
| Limited uptake of HCV treatment in low- and middle-income countries | To the extent that HCV medicines are available at all in low- and middle-income countries, it is mostly Peg-IFN and RBV. These medicines have limited efficacy and significant side-effects. Peg-IFN also requires weekly injections<br>People are not aware that they are infected with HCV<br>Lack of recognition of HCV risks by many people |
| Deterrent effects of the anti-diversion provisions for discounted originator DAAs, where available, and imposed on generic licensees | Burdens on health-care providers and patients to comply with anti-diversion rules<br>Potential disruptions of therapy associated with refills<br>Potential breaches of privacy and confidentiality associated with compliance with anti-diversion provisions |
| Deterrent effects of stigma and discrimination on uptake | Discriminatory attitudes of health-care providers towards people who inject drugs and men who have sex with men<br>Patients' fears of being reported to the authorities in settings where compulsory or coercive drug rehabilitation programmes are in place |

# 8. Potential market interventions

In assessing possible market interventions to improve access to safe, affordable and effective HCV treatments, it is clear that generating robust demand for DAAs is a priority. Clear signals of interest from governments and international donors could accelerate and incentivize the market entry of affordable generics, and could create a virtuous circle whereby orders are large enough to enable affordable prices to be charged that in turn would permit further increases in order volumes – resulting in widespread access to treatment and cure of HCV infection for HIV/HCV coinfected and HCV mono-infected patients.

Creating strong demand for DAAs will also require improved diagnostic tools and strategies, improved strategic data, advocacy for robust funding by donors and national governments, treatment education programmes, and support from civil society, treatment activists and patients' groups to demand lower prices. Demand creation will require long-term investment since removal of existing demand impediments will not occur rapidly.

While investments are made in building demand, work should focus on systematic issues (e.g. ensuring timely uptake of treatment guidelines, building system capacity) and on removing patent barriers to access and affordability. Once demand has been created, consideration should be given to bulk purchasing and other strategies to expedite uptake.

Table 15 suggests opportunities for intervention to address shortcomings in the HCV treatment market outlined in this landscape. Opportunities are not necessarily exclusive to UNITAID and may fall within the mandate and expertise of other market actors.

**Table 15. Potential HCV market interventions**

| Intervention | Market weakness addressed by intervention |
|---|---|
| Support for clinical trials of combination regimens that are not being pursued by industry | Lack of an HCV treatment regimen that satisfies requirements of the target product profile |
| Support for clinical trials evaluating DAA regimens for specific genotypes or patient populations, such as patients with HIV/HCV coinfection or cirrhosis, where industry is not conducting such trials | Lack of an HCV treatment regimen that satisfies requirements of the target product profile |
| Support to WHO to implement a multi-stakeholder process to identify optimal DAA regimens for low- and middle-income countries | Lack of an HCV treatment regimen that satisfies requirements of the target product profile |
| Support to WHO to expedite updates to normative guidance for HCV treatment and to assist national governments in aligning national guidelines with WHO guidance | Potential delays in development of normative guidance |
| Support inclusion of DAAs on WHO Model List of Essential Medicines | Delays associated with regulatory approval processes<br>Uncertain national commitment to purchasing HCV medicines |
| Support countries in negotiating better prices for DAAs | Insufficient availability of SOF at the price of US$ 900 per treatment (as negotiated by Egypt) |
| Support development and publication of patent information on DAAs | Lack of transparency on patent barriers hampers strategies to address those barriers |
| Support opposition to patent applications on SOF and other DAAs | Patent barriers |
| Support countries in using compulsory licensing and other TRIPS flexibilities | Patent barriers |

| | |
|---|---|
| Work with originator companies to improve existing voluntary licensing agreements or to sign new ones | Patent barriers<br>Exclusion of many middle-income countries from voluntary licence agreements |
| Advocacy with more companies to enter into voluntary licensing agreements | Patent barriers |
| Patent buy-out for key DAAs | Patent barriers |
| Advocacy for donor support and cooperation to scale up HCV treatment programmes | Lack of donor programmes for HCV treatment scale-up |
| Support prequalification of DAAs | Lack of competition by and among quality-assured generics |
| Support efforts to increase price transparency | Lack of price transparency hampers price negotiations |
| High-volume bulk purchase of generic DAAs to reduce costs by enhancing economies of scale | Uncertainty regarding volumes limits the scope for price reductions by manufacturers of generic DAAs |
| Support for costing and cost-effectiveness analysis to demonstrate returns on investments in HCV treatment programmes | Lack of donor programmes for scale-up of HCV treatment<br>Uncertain national commitment to purchasing HCV medicines |
| Support to patients' groups and advocates to demand fairer pricing policies for DAAs | Extremely high commercial prices for originator products<br>Negotiated price for SOF in Egypt that is still substantially higher than actual costs of production |
| Support proof-of-concept studies to demonstrate that it is feasible to diagnose and cure HCV infection at minimal cost in low- and middle-income countries (including, but not limited to, integration in HIV programmes) | Lack of donor programmes for HCV treatment scale-up<br>Uncertain national commitment to purchasing HCV medicines |
| Convene consultation with key actors in middle-income countries (e.g. civil society, providers of HCV treatment) to identify strategies to address intellectual property constraints on access to HCV treatment | Patent barriers<br>Exclusion of many middle-income countries in licence agreements |
| Support generic producers (of both APIs and finished products) not licensed by Gilead to develop generic DAAs | Lack of alternatives for generic production of SOF other than Indian manufacturers licensed by Gilead |
| Support to appropriate international or regional body(ies) to facilitate regulatory harmonization for DAAs | Delays in uptake associated with regulatory approval processes |
| Enhance access to HCV diagnosis | Lack of demand for treatment because people are not aware that they are infected with HCV |

# References


1. Global policy report on the prevention and control of viral hepatitis. Geneva: World Health Organization; 2013.
2. Hepatitis C. Fact sheet No 164. Geneva: World Health Organization; 2014.
3. Hepatitis C FAQs for the Public. Atlanta (GA): US Centers for Disease Control and Prevention; 2014.
4. Taylor L, Swan T, Mayer K. HIV coinfection with hepatitis C virus: evolving epidemiology and treatment paradigms. Clinical Infectious Diseases. 2012;55(Supp. 1):S33 – S42.
5. Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014.
6. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57(4):1333 – 42.
7. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of hepatology. 2014;6(1Suppl):S45 – 57.
8. The Gap Report. Geneva: Joint United Nations Programme on HIV/AIDS; 2014.
9. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095 – 128.
10. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(117 – 71).
11. Wandeler G, Gsponer T, Bregenzer A, Gunthard H, Clerc O, Calmy A et al. Hepatitis C virus infections in the Swiss HIV cohort study: a rapidly evolving epidemic. Clinical Infectious Diseases. 2012;15(10):1408 – 16.
12. Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. Journal of hepatology. 2006;45(4):607 – 16.
13. Andreoni M, Giacometti A, Maida I, Meraviglia P, Ripamonti D, Sarmati L. HIV-HCV co-infection: epidemiology, pathogenesis and therapeutic implications. European Review for Medical and Pharmacological Sciences. 2012;16:1473 – 83.
14. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2014;61(1):77 – 87.
15. Garten R, Lai S, Zhang J, Liu W, Chen J, Vlahov D et al. Rapid transmission of hepatitis c virus among young injecting heroin users in Southern China. International Journal of Epidemiology. 2004;33:182 – 8.
16. Quan VM, Go VF, Nam le V, Bergenstrom A, Thuoc NP, Zenilman J et al. Risks for HIV, HBV, and HCV infections among male injection drug users in northern Vietnam: a case-control study. AIDS Care. 2009;21:7 – 16.
17. HCV global prevalence 2013. HCV map. Louisville (CO): Center for Disease Analysis; 2013 (http://www.centerforda.com/map.htm, accessed 02 February 2015.
18. The diagnosis and treatment of hepatitis C: a technical landscape. Geneva: Médecins sans Frontières; 2013.

19. Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver International. 2011;31 Suppl 2:30 – 60.

20. Kershenobich D, Razavi HA, Sanchez – Avila JF, Bessone F, Coelho HS, Dagher L et al. Trends and projections of hepatitis C virus epidemiology in Latin America. Liver International. 2011;31 Suppl 2:18–29.

21. Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver International. 2011;31 Suppl 2:61–80.

22. Keainga S, Dodged J, Norrisa P, Frenche A, Glesbyf M, Edling B et al., editors. The effect of hepatic fibrosis and HCV viremia on serum inflammatory mediators in HIV infection. A women's interagency HIV study. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta (GA), 3 – 6 March 2013.

23. Kaplan RC, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gange SJ et al. T cell activation and senescence predict subclinical carotid artery disease in HIV-infected women. The Journal of Infectious Diseases. 2011;203(4):452–63.

24. Sun HY, Chang SY, Yang ZY, Lu CL, Wu H, Yeh CC et al. Recent hepatitis C virus infections in HIV-infected patients in Taiwan: incidence and risk factors. Journal of Clinical Microbiology. 2012;50(3):781–7.

25. Vivithanaporn P, Maingat F, Lin LT, Na H, Richardson CD, Agrawal B et al. Hepatitis C virus core protein induces neuroimmune activation and potentiates human immunodeficiency virus-1 neurotoxicity. PloS one. 2010;5(9):e12856.

26. Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. Lancet. 2011;377(9772):1198–209.

27. Wilson MG, Chambers L, Bacon J, Rueda S, Ragan M, Rourke SB. Issues of comorbidity in HIV/AIDS: an overview of systematic reviews: Roundtable draft. Toronto: Ontario HIV Treatment Network; 2010.

28. Berenguer J, Alejos B, Hernando V, Viciana P, Salavert M, Santos I et al. Trends in mortality according to hepatitis C virus serostatus in the era of combination antiretroviral therapy. Aids. 2012;26(17):2241–6.

29. Branch AD, Van Natta ML, Vachon ML, Dieterich DT, Meinert CL, Jabs DA et al. Mortality in hepatitis C virus-infected patients with a diagnosis of AIDS in the era of combination antiretroviral therapy. Clinical Infectious Diseases. 2012;55(1):137–44.

30. Crowell TA, Gebo KA, Balagopal A, Fleishman JA, Agwu AL, Berry SA et al. Impact of hepatitis coinfection on hospitalization rates and causes in a multicenter cohort of persons living with HIV. Journal of Acquired Immune Deficiency Syndromes. 2014;65(4):429–37.

31. de Ledinghen V, Barreiro P, Foucher J, Labarga P, Castera L, Vispo ME et al. Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. Journal of Viral Hepatitis. 2008;15(6):427–33.

32. Salmon-Ceron D, Rosenthal E, Lewden C, Bouteloup V, May T, Burty C et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: The French national Mortalité 2005 study. Journal of Hepatology. 2009;50(4):736–45.

33. van der Helm J, Geskus R, Sabin C, Meyer L, Del Amo J, Chene G et al. Effect of HCV infection on cause-specific mortality after HIV seroconversion, before and after 1997. Gastroenterology. 2013;144(4):751–60 e2.

34. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Archives of internal medicine. 2006;166(15):1632–41.

35. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clinical Infectious Diseases. 2001;33(4):562–9.

36. Pineda JA, Romero-Gomez M, Diaz-Garcia F, Giron-Gonzalez JA, Montero JL, Torre-Cisneros J et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. Hepatology. 2005;41(4):779–89.

37. WHO Model List of Essential Medicines. Geneva: World Health Organization; 2013.

38. Patent situation of key products for treatment of hepatitis C. ABT-450. Working paper. Geneva: World Health Organization; 2014.

39. Patent situation of key products for treatment of hepatitis C. Daclatasvir. Working paper. Geneva: World Health Organization; 2014.

40. WHO. Patent situation of key products for treatment of hepatitis C. Dasabuvir. Working paper. Geneva: World Health Organization, 2014.

41. Patent situation of key products for treatment of hepatitis C. Ledipasvir. Working paper. Geneva: World Health Organization; 2014.

42. Patent situation of key products for treatment of hepatitis C. Ombitasvir. Working paper. Geneva: World Health Organization; 2014.

43. Patent situation of key products for treatment of hepatitis C. Simeprevir. Working paper. Geneva: World Health Organization; 2014.

44. Patent situation of key products for treatment of hepatitis C. Sofosbuvir. Working paper. Geneva: World Health Organization; 2014.

45. Gray A. Access to medicines and drug regulation in developing countries: a resource guide for DFID. London: DFID Health Systems Resource Centre; 2004.

46. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. Journal of the American Medical Association. 2004;292(23):2839–48.

47. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. New England Journal of Medicine. 2004;351(5):451–9.

48. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358(9286):958–65.

49. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr. et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. New England Journal of Medicine. 2002;347(13):975–82.

50. Berenguer J, Alvarez-Pellicer J, Martin PM, Lopez-Aldeguer J, Von-Wichmann MA, Quereda C et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology. 2009;50(2):407–13.

51. Mira JA, Rivero-Juarez A, Lopez-Cortes LF, Giron-Gonzalez JA, Tellez F, de los Santos-Gil I et al. Benefits from sustained virologic response to pegylated interferon plus ribavirin in HIV/hepatitis C virus-coinfected patients with compensated cirrhosis. Clinical Infectious Diseases. 2013;56(11):1646–53.

52. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. New England Journal of Medicine. 2012;366(3):216–24.

53. Molina J, Orkin C, Iser D et al, editors. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotypes 1, 2, 3 and 4 infection in patients co-infected with HIV (PHOTON-2). Oral abstract MOAB0105LB. 20th International AIDS Conference, Melbourne, 20 – 25 July 2014.

54. Sulkowski M, Mallolas J, Bourliere M et al, editors. Efficacy and safety of the all-oral regimen, MK-5172-MK-8742 + RBV for 12 weeks in G1 HIV/HCV coinfected patients: the C-WORTHY Study. Oral abstract 63. 49th Annual Meeting of the European Association for the Study of the Liver, London, 9 – 13 April 2014.

55. Sulkowski MS, Naggie S, Lalezari J, Fessel WJ, Mounzer K, Shuhart M et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. Journal of the American Medical Association. 2014;312(4):353–61.

56. Wyles D, Sulkowski M, Eron J et al. TURQUOISE-I: 94% SVR12 in HCV/HIV-1 coinfected patients treated with ABT-450/r/ombitasvir, dasabuvir and ribavirin. Abstract 1939. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November, 2014.

57. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut. 2006;55(9):1350–9.

58. Hadziyannis SJ, Sette H, Jr., Morgan TR, Balan V, Diago M, Marcellin P et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Annals of Internal Medicine. 2004;140(5):346–55.

59. Antaki N, Craxi A, Kamal S, Moucari R, Van der Merwe S, Haffar S et al. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. Liver International. 2010;30(3):342–55.

60. Bruno R, Cariti G, Nasta P, Capetti A, Ravasio V, Galli M et al. OPERA: responses to peginterferon and ribavirin therapy in a subgroup of interferon-naive patients with HIV/HCV genotype 2/3 co-infection in Italy. Liver International. 2015; 35(1):120 – 9.

61. Davies A, Singh KP, Shubber Z, Ducros P, Mills EJ, Cooke G et al. Treatment outcomes of treatment-naive hepatitis C patients co-infected with HIV: a systematic review and meta-analysis of observational cohorts. PloS one. 2013;8(2):e55373.

62. Ford N, Kirby C, Singh K, Mills EJ, Cooke G, Kamarulzaman A et al. Chronic hepatitis C treatment outcomes in low- and middle-income countries: a systematic review and meta-analysis. Bulletin of the World Health Organization. 2012;90(7):540–50.

63. Martin-Carbonero L, Puoti M, Garcia-Samaniego J, De Luca A, Losada E, Quinzan G et al. Response to pegylated interferon plus ribavirin in HIV-infected patients with chronic hepatitis C due to genotype 4. Journal of viral hepatitis. 2008;15(10):710–5.

64. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. New England Journal of Medicine. 2004;351(5):438–50.

65. Win LL, James P, Wong DK. Response-guided therapy for hepatitis C genotype 2 and 3 in those with HIV coinfection. Digestive Diseases and Sciences. 2014;59(8):1946–9.

66. Danilovic DL, Mendes-Correa MC, Chammas MC, Zambrini H, Marui S. Thyroid hormonal disturbances related to treatment of hepatitis C with interferon-alpha and ribavirin. Clinics. 2011;66(10):1757–63.

67. Schreuder TC, Gelderblom HC, Weegink CJ, Hamann D, Reesink HW, Devries JH et al. High incidence of type 1 diabetes mellitus during or shortly after treatment with pegylated interferon alpha for chronic hepatitis C virus infection. Liver International. 2008;28(1):39–46.

68. Talal AH, LaFleur J, Hoop R, Pandya P, Martin P, Jacobson I et al. Absolute and relative contraindications to pegylated-interferon or ribavirin in the US general patient population with chronic hepatitis C: results from a US database of over 45 000 HCV-infected, evaluated patients. Alimentary Pharmacology & Therapeutics. 2013;37(4):473–81.

69. McGowan CE, Monis A, Bacon BR, Mallolas J, Goncales FL, Goulis I et al. A global view of hepatitis C: physician knowledge, opinions, and perceived barriers to care. Hepatology. 2013;57(4):1325–32.

70. Bani-Sadr F, Lapidus N, Melchior JC, Ravaux I, Bensalem M, Rosa I et al. Severe weight loss in HIV/HCV-coinfected patients treated with interferon plus ribavirin: incidence and risk factors. Journal of Viral Hepatitis. 2008;15(4):255–60.

71. Henry DH, Slim J, Lamarca A, Bowers P, Leitz G, HIV/HCV Coinfection Natural History Study Group. Natural history of anemia associated with interferon/ribavirin therapy for patients with HIV/HCV coinfection. AIDS Research and Human Retroviruses. 2007;23(1):1–9.

72. Mira JA, Lopez-Cortes LF, Merino D, Arizcorreta-Yarza A, Rivero A, Collado A et al. Predictors of severe haematological toxicity secondary to pegylated interferon plus ribavirin treatment in HIV-HCV-coinfected patients. Antiviral Therapy. 2007;12(8):1225–35.

73. Pontali E, Angeli E, Cattelan AM, Maida I, Nasta P, Verucchi G et al. Cytopenias during treatment of HIV-HCV-coinfection with pegylated interferon and ribavirin: safety analysis of the OPERA study. Antiviral Therapy. 2014, May 15. doi: 10.3851/IMP2781 [Epub ahead of print].

74. Bani-Sadr F, Carrat F, Rosenthal E, Piroth L, Morand P, Lunel-Fabiani F et al. Spontaneous hepatic decompensation in patients coinfected with HIV and hepatitis C virus during interferon-ribavirin combination treatment. Clinical Infectious Diseases. 2005;41(12):1806–9.

75. Mauss S, Valenti W, DePamphilis J, Duff F, Cupelli L, Passe S et al. Risk factors for hepatic decompensation in patients with HIV/HCV coinfection and liver cirrhosis during interferon-based therapy. Aids. 2004;18(13):F21–5.

76. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH et al. Telaprevir for previously untreated chronic hepatitis C virus infection. New England Journal of Medicine. 2011;364(25):2405–16.

77. Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS et al. Boceprevir for untreated chronic HCV genotype 1 infection. New England Journal of Medicine. 2011;364(13):1195–206.

78. Sulkowski MS, Sherman KE, Dieterich DT, Bsharat M, Mahnke L, Rockstroh JK et al. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. Annals of Internal Medicine. 2013;159(2):86–96.

79. Sulkowski M, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. Lancet Infectious Diseases. 2013;13(7):597–605.

80. Hezode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology. 2014;147(1):132 – 42 e4.

81. Aronsohn A, Jensen D. Expanding access to hepatitis C virus care: a call to deconstruct individualized therapy. Hepatology. 2014;59(1):13–5.

82. Bichoupan K, Martel-Laferriere V, Sachs D, Ng M, Schonfeld EA, Pappas A et al. Costs of telaprevir-based triple therapy for hepatitis C: $189,000 per sustained virological response. Hepatology. 2014;60(4):1187–95.

83. American Association for the Study of Liver Diseases, Infectious Diseases Society of America, International Antiviral Society – USA. Recommendations for testing, managing, and treating hepatitis C (http://www.hcvguidelines.org, accessed 2 February 2015).

84. Merck voluntarily discontinuing VICTRELIS® (boceprevir) 200 mg capsules. Letter by Paul J. Bader, RPh, Director, Pharmacy & Distribution, Merck Sharp & Dohme Corp. posted on USFDA website. January 2015.

85. Weisman R. Vertex to stop selling hepatitis C drug Incivek. Boston Globe. 12 August 2014.

86. Dieterich D, Rockstroh J, Orkin C et al., editors. Simeprevir plus PegIFN/RBV in HCV genotype-1/HIV-1 coinfecdtion. Oral Abstract 24. 21st Conference on Retroviruses and Opportunistic Infections, Boston (MA), 3 – 6 March 2014.

87. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2014;384(9941):403–13.

88. Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2014;384(9941):414–26.

89. Moreno C, Hezode C, Marcellin P et al. Once-daily simeprevir (TMC435) with peginterferon/ribavirin in treatment-naive or treatment-experienced chronic HCV genotpype 4-infected patients: final results of a phase III trial, Poster P1319. 49th Annual Meeting of the European Association for the Study of the Liver, 9 – 13 April, London, 2014.

90. Ioannou GN, Beste LA, Green PK. Similar effectiveness of boceprevir and telaprevir treatment regimens for hepatitis C virus infection on the basis of a nationwide study of veterans. Clinical Gastroenterology and Hepatology. 2014;12(8):1371–80.

91. EASL recommendations on treatment of hepatitis C. Geneva: European Association for Liver Diseases; 2014 (http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C.pdf, accessed 2 February 2015).

92. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014;146(2):430–41 e6.

93. Jensen D, Brunda M, Elston R et al. Interferon-free regimen containing setrobuvir in combination with ritonavir-boosted danoprevir and ribavirin with or without mericitabine in HCV genotype 1 treatment-naive patients: interim results from the ANNAPURNA study. Poster 1098. 64th Annual Meeting of the American Association of Liver Diseases, Washington (DC), 1 – 5 November 2013.

94. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. New England Journal of Medicine. 2014;370(16):1483–93.

95. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. New England Journal of Medicine. 2014;370(20):1889–98.

96. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. New England Journal of Medicine. 2013;368(20):1867–77.

97. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. New England Journal of Medicine. 2014;370(21):1993–2001.

98. Gane E, Stedman C, Garg V et al. editors. An interferon- and ribavirin-free 12-week regimen of once-daily VX-135 and daclatasvir in treatment-naive patients with genotype 1 HCV infection. Poster P1303. 49th Annual Meeting of the European Association for the Study of the Liver, London, 9 – 13 April 2014.

99. Zhao Y, Podos S, Fabrycki I et al., editors. ACH-3422, a novel HCV HS5B RNA polymerase nucleotide inhibitor, demonstrates improved potency over sofosbuvir against HCV genotype-3 replicons in vitro. Poster 1978. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

100. Hernandez D, Zhou N, Ueland J, Monikowski A, McPhee F. Natural prevalence of NS5A polymorphisms in subjects infected with hepatitis C virus genotype 3 and their effects on the antiviral activity of NS5A inhibitors. Journal of Clinical Virology. 2013;57(1):13–8.

101. Poveda E, Wyles DL, Mena A, Pedreira JD, Castro-Iglesias A, Cachay E. Update on hepatitis C virus resistance to direct-acting antiviral agents. Antiviral Research. 2014;108:181–91.

102. McCormick AL, Wang L, Garcia-Diaz A, Macartney MJ, Webster DP, Haque T. Prevalence of baseline polymorphisms for potential resistance to NS5A inhibitors in drug-naive individuals infected with hepatitis C genotypes 1 – 4. Antiviral therapy. 2014, Mar 12. doi: 10.3851/IMP2763 [Epub ahead of print].

103. Dvory-Sobel H, Doehle B, Svarovskaia E et al. The prevalence of HCV NS5A, nucleoside and polymerase inhibitor resistance-associated variants and the effects on treatment with lepidasvir/ sofosbuvir + /- RBV in the phase 3 ION studies. Oral abstract 38. International Workshop on Antiviral Drug Resistance, Berlin, 3 – 7 June 2014.

104. Lawitz E, Poordad F, Gutierrez J et al., editors. Grazoprevir (MK-71712) + sofosbuvir in treatment-naive patients with hepatitis C virus genotype 1 infection, with and without cirrhosis, for durations of 4, 6 or 8 weeks (interim results). 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

105. Gane E, RH H, An D, et al., editors. Ledipasvir/sofosbuvir fixed-dose combination is safe and effective in difficult-to-treat populations including GT3 patients, decompensated GT1 patients, and GT1 patients with prior sofosbuvir experience. Abstract 06. 49th Annual Meeting of the European Association for the Study of the Liver, London, 9 – 13 April 2014.

106. Gane E, Hyland R, An D et al., editors. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection. Abstract LB-11. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

107. Kapoor R, Kohli A, Sidharthan S et al., editors. Treatment of hepatitis C gentoype 4 with ledipasvir and sofosbuvir for 12 weeks: results of the SYNERGY trial. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

108. Cheng G, Peng B, Corsa A et al., editors. Antiviral activity and resistance profile of the novel HCV NS5A inhibitor GS-5885. Abstract 1172. 47th Annual Meeting of the European Association for the Study of the Liver, Barcelona, 18 – 22 April 2012.

109. Muir A, Poordad F, Sheikh A et al., editors. SVR-4 results for the combination of ACH-3102 and sovaprevir, with ribavirin, in patients with genotype 1 chronic hepatitis C infection. Oral abstract LB6. 23rd Annual Conference of the Asian Pacific Association for the Study of the Liver, Brisbane, 12 – 15 March 2014.

110. Muir A, Brennan R, Herring R et al., editors. A single direct-acting antiviral agent, ACH-3102, with ribavirin is able to achieve a robust antiviral response in subjects with genotype 1b chronic hepatitis C infection. Poster abstract 625. 23rd Annual Conference of the Asian Pacific Association for the Study of the Liver, Brisbane, 12 – 15 March 2014.

111. Ng T, Krishnan P, Kati W et al., editors. ABT-530, an HCV NS5A inhibitor with potent pangenotypic activity and high barrier to resistance. Abstract/Poster 639. 21st Conference on Retroviruses and Opportunistic Infections, Boston (MA), 3 – 6 March 2014.

112. Walker J, Crosby R, Wang A, Woldu E, Vamathevan J, Voitenleitner C et al. Preclinical characterization of GSK2336805, a novel inhibitor of hepatitis C virus replication that selects for resistance in NS5A. Antimicrobial Agents and Chemotherapy. 2014;58(1):38–47.

113. Yang G, Patel D, Zhao Y et al., editors. Findings from clinical virology studies on ACH-3102 are consistent with preclinical observations on its improved potency against genotype-1a HCV and resistant variants. Poster Abstract 2403. 48th Annual Meeting of the European Association for the Study of the Liver, Amsterdam, 24 – 28 April 2013.

114. Yeh W, Lipardi C, Jumes P et al., editors. MK-8742, a HCV NS5A inhibitor with a broad spectrum of HCV genotypic activity, demonstrates potential antiviral activity in gentoype-1 and -3 HIV-infected patients. Poster 479. 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington (DC), 1 – 5 November 2013.

115. Asante-Appiah E, Liu R, Curry S et al., editors. MK-8408, a potent and selective NS5A inhibitor with a high genetic barrier to resistance and activity against HCV genotypes 1 – 6. Poster 1979. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

116. Kadow J, Gentles R, Ding M et al., editors. Discovery of BMS-791325, an allosteric NS5B replicase inhibitor for the treatment of hepatitis C. Abstract MEDI 23. 243rd American Chemical Society National Meeting, San Diego (CA), 25 – 29 March 2012.

117. Kohli A, Sims Z, Nelson A et al., editors. Combination oral, hepatitis C antiviral therapy for 6 or 12 weeks: final results of the SYNERGY trial. 21st Conference on Retroviruses and Opportunistic Infections, Boston (MA), 3 – 6 March 2014.

118. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. The New England Journal of Medicine. 2014;370(3):222–32.

119. Lange CM, Zeuzem S. Perspectives and challenges of interferon-free therapy for chronic hepatitis C. Journal of Hepatology. 2013;58(3):583–92.

120. Ruane P, Ain D, Meshrekey R, Riad J, Stryker R, Soliman M et al., editors. Sofosbuvir plus ribavirin, an interferon-free regimen, in the treatment of treatment-naïve and treatment-experienced patients with chronic genotype 4 HCV infection. Abstract P1243. 49th Annual Meeting of the European Association for the Study of the Liver, London, 9 – 13 April 2014.

121. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. New England Journal of Medicine. 2014;370(20):1879–88.

122. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014;384(9956):1756 – 65.

123. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. New England Journal of Medicine. 2014;370(3):211 – 21.

124. Daklinza. European Product Assessment Report (EPAR). Annex I: Summary of product characteristics. London: European Medicines Agency; 2014.

125. Eley T, You X, Wang R et al., editors. Daclatasvir: overview of drug-drug interactions with antiretroviral agents and other common concomittant drugs. Poster 63. HIV DART (Frontiers in Drug Development for Antiretroviral Therapies), Key Biscayne (FL), 9 – 12 December 2014.

126. Everson G, Tran T, Towner W et al., editors. Safety and efficacy of treatment with interferon-free, ribavirin-free combination of sofosbuvir + GS-5816 in treatment-naive patients with genotypes 1-6 HCV infection. Oral abstract 111. 49th Annual Meeting of the European Association for the Study of the Liver, London, 9 – 13 April 2014.

127. Tran T, Morgan T, Thuluvath P et al., editors. Safety and efficacy of treatment with sofosbuvir + GS-5816 + /-ribavirin for 8 or 12 weeks in treatment naive patients with gentoype 1-6 HCV infection. Abstract 80. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

128. Gane E, Kocinsky C, Schwabe C et al., editors. Interim sustained virologic response (SVR), safety and tolerability results of 8-week treatment with ACH-3102 and sofosbuvir in chronic hepatitis C (HCV), genotype-1 (GT-1), treatment-naive patients: a Phase 2 "proxy" study. Abstract LB-23. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

129. Ferenci P, Bernstein D, Lalezari J et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HIV. New England Journal of Medicine. 2014;370(21):1983–92.

130. Pharmaceutical Sector Inquiry. Final Report. Brussels: European Commission; 8 July 2009.

131. Pollack A. Gilead's hepatitis C drug, Sovaldi, is on pace to become a blockbuster. New York Times, 23 July 2014 (http://www.nytimes.com/2014/07/24/business/sales-of-hepatitis-c-drug-sovaldi-soar.html?_r=0, accessed 2 February 2015).

132. Silverman E. Ooh La La: France negotiates a steep discount for Sovaldi from Gilead. Wall Street Journal, 20 November 2014. (http://blogs.wsj.com/pharmalot/2014/11/20/ooh-la-la-france-negotiates-a-steep-discount-for-sovaldi/, accessed 2 February 2015).

133. Zarzalejos A. Simeprevir: la mejor noticia en los ultimos 25 anos para los pacientes de hepatitis C. El Confidencial, 28 July 2014 (http://www.elconfidencial.com/sociedad/2014-07-28/simeprevir-la-mejor-noticia-en-los-ultimos-25-anos-para-los-pacientes-de-hepatitis-c_166679/, accessed 2 February 2015).

134. NICE consults on draft guidance on the drug simeprevir (Olysio) for treating hepatitis C. FiercePharma Marketing; 2014 (http://www.fiercepharmamarketing.com/press-releases/nice-consults-draft-guidance-drug-simeprevir-olysio-treating-hepatitis-c, accessed 31 January 2015).

135. Un médicament contre l'hépatite C à 685 francs la pilule. Le Matin, 8 August 2014.

136. Knox R. WHO calls for high-priced drugs for millions with hepatitis C. National Public Radio, 9 April 2014 (http://www.npr.org/blogs/health/2014/04/09/300959958/who-recommends-high-priced-drugs-for-millions-with-hepatitis-c, accessed 2 February 2015).

137. Hearing on hepatitis C in veterans. Testimony of Michael Valentino, VA Chief Consultant for Pharmacy Benefits Management. Hearing before the Committee on Veterans Affairs, United States Senate 2014.

138. Forette C. Gilead's license on hepatitis C drugs, sofosbuvir and ledispavir: a fool's bargain. Hep-Coalition, 10 October 2014 (http://www.hepcoalition.org/news/article/gilead-s-license-on-hepatitis-c, accessed 2 February 2015).

139. Kaplan K. Activists hold die-in to protect high price of Gilead's hepatitis C drug (Press release). Treatment Action Group, 24 July 2014 (http://www.treatmentactiongroup.org/hcv/gilead-die-in, accessed 2 February 2015).

140. Dickson V. Sovaldi likely to cost Medicare billions. Modern Healthcare, 29 July 2014 (http://www.modernhealthcare.com/article/20140729/BLOG/307299997, accessed 2 February 2015).

141. Roy A. The Sovaldi tax: Gilead can't justify the price it's asking for hepatitis C treatment. Forbes, 17 June 2014 (http://www.forbes.com/sites/theapothecary/2014/06/17/the-sovaldi-tax-gilead-cant-justify-the-price-its-asking-americans-to-pay/, accessed 2 February 2014).

142. Pollack A. AbbVie deal heralds changed landscape for hepatitis drugs. New York Times, 22 December 2014 (http://www.nytimes.com/2014/12/22/business/pharmacy-deal-heralds-changed-landscape-for-hepatitis-drugs.html?_r=0, accessed 2 February 2015).

143. Dennis M. Gilead's hepatitis C drug Harvoni selected by health insurer Anthem. FirstWord Pharma, 9 January 2015 (http://www.firstwordpharma.com/node/1256115#axzz3PGYH5dLX, accessed 2 February 2015).

144. Fick M, Herschler B. Gilead offers Egypt new hepatitis C drug at 99 percent discount. Reuters, 21 March 2014 (http://www.reuters.com/article/2014/03/21/us-hepatitis-egypt-gilead-sciences-idUSBREA2K1VF20140321, accessed 2 February 2015).

145. Health ministry: more than 100 000 Egyptians applied for 'miracle' hepatitis C drug. Mada Masr, 19 September 2014. (http://www.madamasr.com/news/health-ministry-more-100000-egyptians-applied-miracle-hepatitis-c-drug, accessed 2 February 2015).

146. Gilead Sciences offers the Government of Mongolia its "Sovaldi" drug for the treatment of chronic hepatitis C virus. InfoMongolia.com, 2014 (http://www.infomongolia.com/ct/ci/7948, accessed 2 February 2015)

147. Patent landscape report for pegylated interferon alfa 2A & 2B. New York: Initiative for Medicines, Access and Knowledge; 2013.

148. Milani B, Gaspani S. Pathway to affordable, quality-assured sources of pegylated interferon alpha for treating hepatitis C. Generics and Biosimilars Initiative Journal. 2013;2(4):194–203.

149. Loftus P. Lucrative drug niche sparks legal scramble. Wall Street Journal, 20 July 2014 (http://www.wsj.com/articles/lucrative-drug-niche-sparks-legalscramble-1405898259, accessed 2 February 2015).

150. I-MAK files patent challenge on hepatitis C drug sofosbuvir in India. New York: Initiative for Medicines, Access and Knowledge; 2013 (http://www.i-mak.org/i-mak-blog-updates/2013/11/22/i-mak-files-patent-challenge-on-hepatitis-c-drug-sofosbuvir.html, accessed 2 February 2015).

151. Subbu R. Natco moves to oppose Gilead hepatitis C drug patent. The Hindu, 12 April 2014.

152. Médecins Sans Frontières. Patent Opposition database. Sofosbuvir (GS7977). (http://patentoppositions.org/drugs/51dfee9097961f0002000020, accessed 23 January 2015).

153. Gilead expands hepatitis C generic licensing agreements to include investigational pan-genotypic agent. Business Wire, 26 January 2015.

154. Barooah SP. Gilead to appeal Sofosbuvir patent rejection. SpicyIP, 16 January 2015 (http://spicyip.com/2015/01/gilead-to-appeal-sofosbuvir-patent-rejection.html, accessed 26 January 2015).

155. Dennis M. Gilead to appeal India's rejection of Sovaldi patent. FirstWord Pharma, 16 January 2015 (http://www.firstwordpharma.com/node/1257793#axzz3QcYOdCDf, accessed 26 January 2015).

156. Gilead to challenge hepatitis C drug patent rejection decision. The Economic Times, 16 January 2015 (http://articles.economictimes.indiatimes.com/2015-01-16/news/58149596_1_sovaldi-sofosbuvir-patent-application, accessed 26 January 2015).

157. Presidio Pharmaceuticals licenses clinical stage hepatitis C virus (HCV) NS5A inhibitor to Pharco Pharmaceuticals PPI-668. Bay City Capital, 10 November 2014 (http://baycitycapital.com/portfolio-news/presidio-pharmaceuticals-licenses-clinical-stage-hepatitis-c-virus-hcv-ns5a-inhibitor-pharco-pharmaceuticals-ppi-668/, accessed 25 January 2015).

158. Hill A, Khoo S, Fortunak J et al. Minimum costs for producing hepatitis C direct acting antivirals, for use in large-scale treatment access programs in developing countries. Clinical Infectious Diseases. 2014;58(7):928–36.

159. Van de Ven N, Fortunak J, Simmons B et al. Minimum target prices for production of direct acting antivirals and associated diagnostics to combat hepatitis C virus. Hepatology. 2014 Dec 6. doi: 10.1002/hep.27641. [Epub ahead of print] .

160. Sovaldi dispense report. W6. Cairo: Ministry of Health; 2014.

161. Chaudhry A. Sovaldi – 'miracle' hepatitis C oral drug gets official nod. Dawn, 21 November 2014.

162. Sovaldi in Pakistan: price, availability of hepatitis-C medicine. Healthcare Information Network, 22 January 2015 (http://healthncare.info/sovaldi-pakistan-price-availability-latest-news-hcv-treatment/, accessed 2 February 2015).

163. Bruggmann P, Berg T, Øvrehus A et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. Journal of Viral Hepatitis. 2014;Suppl 1:5 – 33.

164. Fast track: ending the AIDS epidemic by 2030. Geneva: Joint United Nations Programme on HIV/AIDS; 2014.

165. PEPFAR. 2013 report on costs of treatment in the President's Emergency Plan for AIDS Relief (PEPFAR). Washington (DC): Department of State; 2013.

166. Global Fund and hepatitis C treatment. Prepared for the 32nd Board Meeting. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2014.

167. PEPFAR. Technical considerations provided by PEPFAR technical working groups for FY2013 COPS and ROPS. Washington (DC): Department of State; 2013.

168. Hepatitis C diagnostics technology landscape. Geneva: UNITAID; 2015.

169. MSF Access Campaign. Barriers to access and scale up of hepatitis C (HCV) treatment: Gilead's anti-diversion program. Geneva: Médecins Sans Frontières; 2014.

170. Gilead license agreement (full text). Washington (DC): Knowledge Ecology International; 2014 (http://keionline.org/sites/default/files/GILD_Sof_License_Agmt_(FINAL).pdf, accessed 31 January 2015).

171. Osinusi A, Townsend K, Nelson A et al. e, editors. High efficacy of sofosbuvir/ledispasvir for the treatment of HCV genotype 1 in patients coinfected with HIV on or off antiretroviral therapy. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

172. Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. Journal of the American Medical Association. 2013;310(8):804 – 11.

173. Esmat G, Shiha G, Omar R et al., editors. Sofosbuvir plus ribavirin in the treatment of Egyptian patients with chronic genotype 4 HCV infection. Poster 959. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

174. Nelson D, Cooper J, Lalezari J et al., editors. All-oral 12-week combination treatment with daclatasvir (DCV) and sofosbuvir (SOF) in patients infected with HCV genotype (GT) 3: ALLY-3 phase 3 study. Abstract LB-3. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

175. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC et al. Sofosbuvir for previously untreated chronic hepatitis C infection. New England Journal of Medicine. 2013;368(20):1878 – 87.

176. Pianko S, Flamm S, Shiffman M et al., editors. High efficacy of treatment with sofosbuvir + GS-5816 + /- RBV for 12 weeks in treatment-experienced patients with HCV genotype 1 or 3 infection. Abstract 107. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

177. Gane E, Hyland R, An D, al. e, editors. Once-daily sofosbuvir with GS-5816 for 8 weeks with or without ribavirin in patients with HCV genotype 3 without cirrhosisresult in high rates of SVR12: The ELECTRON-2 study. Abstract 79. 65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston (MA), 7 – 11 November 2014.

178. Gilead Sciences. Sovaldi® registration in the developing world. 9 December 2014 (http://www.gilead.com/~/media/Files/pdfs/other/Sovaldi%20Registration%20%20121114.pdf, accessed 20 January 2015).

179. Approval of import of Sovaldi acted as fuel to fire. MM Securities, 2 October 2014 (http://investorguide360.com/wp-content/uploads/2014/10/MMSPL-Research.pdf, accessed 2 February 2015).

180. Registration of Sovaldi: a breakthrough for Ferozsons Lab. MM Securities, 2 October 2014 (http://investorguide360.com/wp-content/uploads/2014/10/MMSPL-Research.pdf, accessed 25 January 2015).

181. Patent situation of key products for treatment of hepatitis C. Sofosbuvir. Geneva: World Health Organization; 2015 (forthcoming).

182. Basu S. Senate Committee Chairman decries high costs for potential HCV cure. US Medicine, January 2015 (http://www.usmedicine.com/agencies/department-of-veterans-affairs/senate-committee-chairman-decries-high-costs-for-potential-hcv-cure/, accessed 25 January 2015).

183. Investigation results: simeprevir sodium. Tokyo: Pharmaceuticals and Medical Devices Agency; 2014 (http://www.pmda.go.jp/english/service/pdf/revision/20141024-simeprevir.pdf, accessed 2 February 2015).

184. Ignjatovic T, Haydock M. Hepatitis C pricing and reimbursement. Datamonitor Healthcare, 12 January 2015 (http://www.datamonitorhealthcare.com/hepatitis-c-pricing-and-reimbursement/, accessed 2 February 2015).

# ANNEXES

## Annex 1. Hepatitis C medicines on the market and in the pipeline (Phase II and beyond)

| Phase[1] | Class | INN | Code | Company |
|---|---|---|---|---|
| Launched | Interferon | peginterferon alfa-2b | | Merck |
| Launched | Interferon | peginterferon alfa-2a | | Roche |
| Launched | NS3/4A inhibitor | boceprevir | | Merck |
| Launched | NS3/4A inhibitor | telaprevir | | Vertex |
| Launched | Nucleoside analogue | ribavirin | | everal companies |
| 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 |
| III | Cyclophilin inhibitor | alisporivir | DEB-025 | Novartis |
| III | Non-nucleoside NS5B inhibitor | beclabuvir | BMS-791325 | Bristol-Myers Squibb |
| III | NS3/4A inhibitor | grazoprevir | MK-5172 | Merck |
| III | NS5A inhibitor | elbasvir | MK-8742 | Merck |
| III | NS5A inhibitor | | GS-5816 | Gilead |
| II | Cyclophilin inhibitor | | SCY-635 | Scynexis |
| II | miR-122 inhibitor | miravirsen | | Santaris Pharma |
| II | Non-nucleoside NS5B inhibitor | | GS-9669 | Gilead |
| II | Non-nucleoside NS5B inhibitor | setrobuvir | ANA-598 | Anadays |
| II | Non-nucleoside NS5B inhibitor | | TMC-647055 | Janssen |
| II | NS3/4A inhibitor | | GS-9256 | Gilead |
| II | NS3/4A inhibitor | vedroprevir | GS-9451 | Gilead |
| II | NS3/4A inhibitor | | ABT-493 | AbbVie |
| II | NS3/4A inhibitor | sovaprevir | ACH-1625 | Achillion |
| II | NS3/4A inhibitor | danoprevir | RG-7227 | Roche |
| II | NS5A inhibitor | | ACH-3102 | Achillion |
| II | NS5A inhibitor | | ABT-530 | AbbVie |
| II | NS5A inhibitor | | GSK-2336805 | GlaxoSmithKline |
| II | NS5A inhibitor | samatasvir | MK-1894 (IDX-719) | Merck (Idenix) |
| II | NS5A inhibitor | | JNJ56914845 (GSK 2336805) | Janssen |
| II | NS5A inhibitor | | PPI-668 | Presidio Pharma |
| II | Nucleoside NS5B inhibitor | mericitabine | RG-7128 | Roche |
| II | Nucleoside NS5B inhibitor | | VX-135 | Vertex |

1 Launched means the product has been launched in at least one country.

## Annex 2. Overview of sustained virological response with sofosbuvir-based combination regimens

The tables in this Annex provide an overview of efficacy data (SVR) for interferon-free sofosbuvir-based regimens in HCV mono-infection and HIV/HCV coinfection *[53, 55, 97, 106, 121–123, 126, 127, 171–177]*.

Data for HIV/HCV coinfection are in red.

The results relate to treatment-naïve, non-cirrhotic study participants, unless otherwise indicated. SVR is usually lower in persons with cirrhosis, especially if they are treatment-experienced (TX-EPX).

A high-level summary of the data presented in this Annex can be found in Table 6 of this report.

### Table A. HCV genotype 1

| | Regimen | SVR for HCV genotype 1 | | |
|---|---|---|---|---|
| | | 8 weeks | 12 weeks | 24 weeks |
| a | **SOFOSBUVIR + RIBAVIRIN**<br>**APPROVED** | | | 68% (17/25)<br>**HIV/HCV: 76% (87/114) to 88% (84/95)** |
| b | **SOFOSBUVIR + DACLATASVIR**<br>**(RBV-free arms only)**<br>**PHASE III** | | 95% (39/41)<br>**HIV/HCV: study underway** | 96.5% (28/29)<br>TX-EXP: 100% (21/21) |
| c | **HARVONI® (SOFOSBUVIR/ LEDIPASVIR) with or without RBV**<br>**APPROVED** | **Without RBV** 94% (202/215)<br>**No data on HIV/HCV** | **Without RBV** 96% (208/216) to 99% (210/213)<br>**HIV/HCV 98% (49/50)**<br>**12-week or 24-week studies planned or underway** | |
| d | **SOFSOBUVIR + GS-5816**<br>**PHASE III (100 mg dose only)** | **100 mg**<br>90% (26/29)<br>**100 mg + RBV**<br>81% (25/31)<br>**No data on HIV/HCV** | **100 mg** 100% (28/28)<br>TX-EXP 100% (27/27)<br>**100mg + RBV**<br>TX-EXP 96% (27/28)<br>**No data on HIV/HCV** | |
| e | **SOFOSBUVIR + SIMEPREVIR**<br>**APPROVED** | Includes non-cirrhotic null responders (Group 1), and treatment-naïve and null responders with F3 and F4 (pre-cirrhosis and cirrhosis) (Group 2) | | |
| | | | **Without RBV**<br>Group 1: 93% (13/14)<br>Group 2: 93% (13/14)<br>**+ RBV**<br>Group 1: 96% (26/27)<br>Group 2: 93% (25/27)<br>**No data on HIV/HCV** | **Without RBV**<br>Group 1: 93% (14/15)<br>Group 2: 100% (16/16)<br>**+ RBV**<br>Group 1: 79% (19/24)<br>Group 2: 93% (28/30<br>**No data on HIV/HCV** |

## Table B. HCV genotype 2

| | Regimen | SVR for HCV genotype 2 | | |
|---|---|---|---|---|
| | | 8 weeks | 12 weeks | 24 weeks |
| a | **SOFOSBUVIR + RIBAVIRIN**<br>**APPROVED** | | 93% (68/72)<br>**HIV/HCV 88% (23/26) and (22/25)** | |
| b | **SOFOSBUVIR + DACLATASVIR (RBV-free arms only)**<br>**PHASE III** | | **HIV/HCV study underway** | 100% (17/17) |
| c | **HARVONI® (SOFOSBUVIR/ LEDIPASVIR) with or without RBV**<br>**APPROVED** | **Not studied for HCV**<br>**Not studied for HIV/HCV** | | |
| d | **SOFOSBUVIR + GS-5816**<br>**PHASE III (100 mg dose only)** | **100 mg**<br>88% (23/26)<br>**100 mg + RBV**<br>88% (23/26)<br>**No data on HIV/HCV** | **100 mg**<br>100% (10/10)<br>**No data on HIV/HCV** | |

## Table C. HCV genotype 3

| | Regimen | SVR for HCV genotype 3 | | |
|---|---|---|---|---|
| | | 8 weeks | 12 weeks | 24 weeks |
| a | **SOFOSBUVIR + RIBAVIRIN**<br>**APPROVED** | | 56% (102/183)<br>**HIV/HCV 67% (24/42)** | 94% (86/92)<br>**HIV/HCV 89% (94/106)** |
| b | **SOFOSBUVIR + DACLATASVIR (RBV-free arms only)**<br>**PHASE III** | | 97% (73/75)<br>58% (11/19) cirrhosis<br>94% (32/34) TX-EXP<br>69% (9/13) TX-EXP + cirrhosis<br>**HIV/HCV study underway** | 89% (16/18)<br>**No data on HIV/HCV** |
| c | **HARVONI® (SOFOSBUVIR/ LEDIPASVIR) with or without RBV**<br>**APPROVED** | | **Without RBV** 65% (16/25)<br>**+ RBV:** 100% (26/26)<br>89% (25/28) **+ RBV** TX-EXP<br>73% (16/22) **+ RBV** TX-EXP + cirrhosis<br>**No data on HIV/HCV** | |
| d | **SOFSOBUVIR + GS-5816**<br>**PHASE III (100 mg dose only)** | **100 mg**<br>96% (26/27)<br>**100 mg + RBV**<br>100% (26/26)<br>**No data on HIV/HCV** | **100 mg**<br>93% (27/27) and 96% (26/27)<br>88% (23/26) TX-EXP + cirrhosis<br>**100 mg + RBV**<br>100% (26/26) TX-EXP<br>96% (25/26) TX-EXP + cirrhosis<br>**No data on HIV/HCV** | |

### Table D. HCV genotype 4

| | Regimen | HCV genotype 4: duration and SVR | |
|---|---|---|---|
| | | 12 weeks | 24 weeks |
| a | **SOFOSBUVIR + RIBAVIRIN**<br>**APPROVED** | 84% (21/25)<br>70% (19/27) TX- EXP<br>**No data on HIV/HCV** | 92% (22/24)<br>89% (24/27) TX-EXP<br>**HIV/HCV** 84% (26/31) |
| b | **SOFOSBUVIR + DACLATASVIR (RBV-free arms only)**<br>**PHASE III** | Study underway HCV<br>**HIV/HCV study underway** | |
| c | **HARVONI®**<br>**(SOFOSBUVIR/ LEDIPASVIR) with or without RBV**<br>**APPROVED** | **Without RBV** 95% (20/21)<br>**HIV/HCV study underway** | |
| d | **SOFSOBUVIR + GS-5816**<br>**PHASE III (100 mg dose only)** | 86% (6/7)<br>**No data on HIV/HCV** | |

### Table E. HCV genotypes 5 and 6

| | Regimen | HCV genotype 5: duration and SVR | HCV genotype 6: duration and SVR |
|---|---|---|---|
| a | **SOFOSBUVIR + RIBAVIRIN**<br>**APPROVED** | **No data in HCV**<br>**No data on HIV/HCV** | **No data in HCV**<br>**No data on HIV/HCV** |
| b | **SOFOSBUVIR + DACLATASVIR (RBV-free arms only)**<br>**PHASE III** | **12-week** studies underway for HCV and **HIV/HCV** | **12-week** studies underway for HCV and **HIV/HCV** |
| c | **HARVONI®**<br>**(SOFOSBUVIR/ LEDIPASVIR) with or without RBV**<br>**APPROVED** | **No data on HCV**<br>**No data on HIV/HCV** | **12 weeks without RBV**<br>96% (24/25) includes TX-EXP (n = 2)<br>**No data on HIV/HCV** |
| d | **SOFSOBUVIR + GS-5816**<br>**PHASE III** | **12 weeks**<br>**25 mg** 100% (1/1)<br>**No data on HIV/HCV** | **12 weeks**<br>**100 mg** 100% (6/6)<br>**No data on HIV/HCV** |

## Annex 3. Summary assessment of selected DAA regimens against target product profiles

The table below, based on currently available data, provides a preliminary assessment of selected DAA regimens against the target product profile. The selected regimens are either approved or in late-stage development.**

| TPP | Universal | | Safe, Tolerable | | Simple | | | Effective, Durable | Cautions |
|---|---|---|---|---|---|---|---|---|---|
| Regimen/ sponsor/ status | Pan-genotypic | Studied in co-infected | Safe, effective in compensated cirrhosis; % SVR | Acceptable, tolerable | Manageable drug–drug interactions with WHO-recommended ARVs | Duration ≤12 weeks | QD | SVR ≥90% | |
| FDC: Viekirax® (ABT-267/ ABT-333/ABT-450/r) + RBV<br>USFDA approved<br>*AbbVie* | NO<br>Genotypes 1 and 4 | YES | YES<br>90–97% | YES | Limited options | YES | NO | YES | Genotyping and possibly subtyping needed; longer treatment may be needed for cirrhosis; BID; ribavirin necessary for genotype 1a; propensity for drug–drug interactions; no paediatric data; RBV contraindicated during pregnancy and nursing |
| Asunaprevir + daclatasvir<br>Approval expected Q4 2014<br>*BMS* | NO<br>Genotype 1b only | YES | YES<br>84% | YES | NO | NO | NO | NO | Genotyping and subtyping required; 24-week regimen; BID; no paediatric data |
| FDC: Asunaprevir + BMS-791325 + daclatasvir<br>Approval expected 2015/2016<br>*Bristol-Myers Squibb* | NO<br>Genotype 1 | NO | YES<br>71–100% (small sample size; phase III trials underway) | YES | Data not available | YES | NO | YES | Genotyping required; BID; phase III underway; ribavirin may be needed |
| Daclatasvir + sofosbuvir<br>Approved in the EU; FDA approval expected Q4 2014<br>*Bristol-Myers Squibb* | Studied in genotypes 1, 2 and 3; phase III trials underway in all HCV genotypes) | Trial underway | YES<br>(both drugs studied separately; trial in cirrhosis underway) | YES | Daclatasvir dose adjustment needed with certain ARVs | Possibly | YES | YES | Data on each drug supports use in cirrhosis, HIV/ HCV (phase III trials in all genotypes, HIV/HCV and cirrhosis underway); no paediatric data |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| FDC: Harvoni®<br>Sofosbuvir/ ledipasvir<br>Approved<br>*Gilead* | NO<br>Genotype1; also studied in genotypes 3, 4 and 6 | YES | YES;<br>65–100%;<br>SVR higher with 24 weeks of treatment | YES | Limited options; drug–drug interactions with tenofovir and efavirenz | YES | YES | YES | Genotyping required; no paediatric data; longer treatment may be needed in cirrhosis |
| FDC: Sofosbuvir/ GS-5816<br>Approval expected 2015/2016<br>*Gilead* | YES | YES | Trials underway | YES | ? | YES | YES | YES | Phase III underway |
| Sofosbuvir + RBV<br>Approved 2013/2014<br>*Gilead* | YES | YES | YES | YES | YES | Only in genotype 2; 24 weeks for genotypes 1,3 and 4; optimal duration for genotypes 5 and 6 not known | NO | YES, except for genotype 1 (see Table A in Annex 2) | Genotyping required; 24-week duration in genotypes 1, 3 and 4; limited data in genotypes 5 and 6; RBV contraindicated during pregnancy and nursing |
| Sofosbuvir + PEG-IFN/RBV<br>Approved 2013/2014<br>*Gilead/Roche/Merck/ generics* | YES | YES | YES | Possibly | YES | YES | NO | YES | Poor tolerability; cold chain required; injections and more intensive monitoring needed; RBV contraindicated during pregnancy and nursing |
| Sofosbuvir + simeprevir (off-label)<br>Approved 2013/2014<br>*Gilead/Janssen* | NO | YES | YES | YES | NO | NO<br>(24 weeks for cirrhosis) | YES | YES | Genotyping required; significant drug–drug interactions; not recommended in advanced cirrhosis (Child-Pugh Class B or Class C); phase III underway |
| MK-5172 + MK-8742<br>Approval expected 2015/2016<br>*Merck* | NO<br>Trial in genotypes 4, 5 and 6 planned; (trial in genotype 3 with sofosbuvir underway) | YES | YES | YES | NO | ? | YES | YES | Genotyping required; propensity for drug–drug interactions |

** There are no data on pregnancy or paediatrics (a study of sofosbuvir/RBV in paediatrics is ongoing), and sponsors do not disclose cold chain requirements prior to approval.
Note: QD = once a day; BID = twice a day.

## Annex 4. Registration status of sofosbuvir in developing countries

The table below provides an overview of the registration status of SOF in developing countries as of 9 December 2014.

| | Low-income countries | Lower-middle-income countries | Upper-middle-income countries |
|---|---|---|---|
| Registered | Egypt | -- | -- |
| Registration pending (application filed) | Tanzania<br>Uganda | Bolivia<br>India<br>Mongolia<br>Nigeria<br>Pakistan*<br>Philippines | Argentina<br>Brazil<br>Mexico<br>Thailand |
| Registration planned or registration file under preparation | Haiti<br>Kenya<br>Mozambique<br>Myanmar | Cameroon<br>El Salvador<br>Guatemala<br>Indonesia<br>Uzbekistan<br>Viet Nam | Colombia<br>Dominican Republic<br>Ecuador<br>Peru<br>South Africa<br>Venezuela |

*Source:* Gilead. Sovaldi® registration in the developing world. December 2014. http://www.gilead.com/~/media/Files/pdfs/other/Sovaldi%20Registration%20%20121114.pdf (accessed 20 Jan 2014).

* According to several sources, SOF was registered in Pakistan in September 2014 *[162, 179, 180]*. However, according to Gilead *[178]*, registration is pending (as of 9 December 2014).

## Annex 5. Summary of the available patent information of 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.[19]

| | Argentina | ARIPO | Brazil | Chile | China | Colombia | Costa Rica | EAPO | Ecuador | Egypt | Ethiopia | Georgia | India | Indonesia | Iran | Jordan | Lebanon | Malaysia | Mexico | Morocco | Nigeria | OAPI | Pakistan | Peru | Philippines | South Africa | Thailand | Tunisia | Ukraine | Uruguay | Venezuela | Viet Nam | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| simeprevir | G | G | F | • | G | • | F | G | F | F | • | • | F | • | • | • | • | G | F | • | • | • | • | F | F | • | • | • | • | F | • | • | |
| | G | F | F | F | G | F | • | G | F | • | • | • | G | • | • | • | • | • | F | • | • | • | • | • | F | G | • | • | F | F | • | F | |
| sofosbuvir | F | • | F | G | G | F | • | • | | • | F* | • | -- | F* | G | • | • | • | G | G | • | • | -- | • | • | G | G | • | -- | • | • | • | • | Harvoni |
| | F | G | G | G | F | F | F | F | | • | F | • | -- | F** | F | • | • | • | F | F | F | • | G | F | F | • | G | F | -- | F | F | • | F | |
| ledipasvir | F | G | • | • | F | F | • | F | | F | • | • | • | F | • | • | • | • | • | F | • | • | • | • | F | • | G | • | • | F | F | • | F | |
| | G | • | • | • | • | • | • | • | | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | F | • | • | • | F | • | • | |
| daclatasvir | F | -- | F | G | G | G | -- | G | | -- | F | -- | -- | F | -- | -- | -- | G | -- | G | -- | -- | -- | -- | G | -- | G | F | -- | -- | -- | F | -- | |
| | F | • | F | • | F | F | • | G | | • | F | • | • | F | • | • | • | • | • | F | • | • | • | • | F | F | G | F | • | • | F | • | F | |
| paritaprevir | G | • | F | • | F | • | • | • | • | • | • | • | F | • | • | • | • | • | F | • | • | • | • | F | • | G | • | • | • | F | • | • | Viekira Pak |
| ombitasvir | F | • | • | • | F | F | • | F | F | • | • | • | F | • | • | • | • | • | F | • | • | • | • | F | • | G | • | • | F | F | • | F | |
| | F | • | • | • | F | F | F | F | • | • | • | • | • | • | • | • | • | • | F | • | • | • | • | F | • | G | F | • | F | F | • | F | |
| dasabuvir | • | • | • | • | F | • | • | • | • | • | • | • | F | • | • | • | • | • | F | • | • | • | • | • | • | G | • | • | • | • | • | • | |
| | G | • | • | • | F | F | F | F | • | • | • | • | F | • | • | • | • | F | F | • | • | • | • | F | F | G | • | • | • | F | • | F | |

G = patent(s) granted; F = patent(s) filed/pending; -- = no patent/no patent application; • = data not available; * patent rejected but under appeal; ** some patents granted according to Gilead voluntary licence *[170]*.

For each molecule, the first row relates to the primary patent; the second row combines information for all other identified patents (except sofosbuvir, where the first row combines information for several patents that are believed to be blocking patents, and paritaprevir, where no other patents have been identified). Instances where one or more patents are granted and one or more others are filed or pending, are marked "G" (granted).

= included in voluntary licenses; = voluntary licence announced.

ARIPO = African Regional Intellectual Property Organization (16 countries); EAPO = Eurasian Patent Organization (8 countries); www
OAPI = Organisation Africaine de la Propriété Intellectuelle (African Intellectual Property Organization) (16 countries).

19 Source of data: WHO *[38–43, 181]*.

## Annex 6. Overview of countries included in voluntary licences

| Country | SOF, LDV, GS-5816 (Gilead) | DCV (Bristol-Myers Squibb) |
|---|---|---|
| Afghanistan | Yes | Yes |
| Angola | Yes | Yes |
| Antigua and Barbuda | Yes | --- |
| Bangladesh | Yes | Yes |
| Benin | Yes | Yes |
| Bhutan | Yes | Yes |
| Bolivia | 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 |
| 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 |
| Egypt | Yes | --- |
| Equatorial Guinea | Yes | Yes |
| Eritrea | Yes | Yes |
| Ethiopia | Yes | Yes |
| Fiji | Yes | Yes |
| Gabon | Yes | Yes |
| Gambia | Yes | Yes |
| Ghana | Yes | Yes |
| Guatemala | Yes | Yes |
| Guinea | Yes | Yes |
| Guinea-Bissau | Yes | Yes |
| Guyana | Yes | Yes |
| Haiti | Yes | Yes |
| Honduras | Yes | Yes |
| India | Yes | Yes |
| Indonesia | Yes | Yes |
| Kenya | Yes | Yes |
| Kiribati | Yes | Yes |
| Kyrgyzstan | Yes | Yes |
| Lao People's Democratic Republic | Yes | Yes |
| Lesotho | Yes | Yes |
| Liberia | Yes | Yes |
| Madagascar | Yes | Yes |

| Country | SOF, LDV, GS-5816 (Gilead | DCV (Bristol-Myers Squibb) |
|---|---|---|
| Malawi | Yes | Yes |
| Maldives | Yes | Yes |
| Mail | Yes | Yes |
| Mauritania | Yes | Yes |
| Mauritius | Yes | Yes |
| Mongolia | Yes | Yes |
| Mozambique | Yes | Yes |
| Myanmar | Yes | Yes |
| Namibia | Yes | Yes |
| Nauru | Yes | Yes |
| Nepal | Yes | Yes |
| Nicaragua | Yes | Yes |
| Niger | Yes | Yes |
| Nigeria | Yes | Yes |
| Pakistan | Yes | Yes |
| Palau | Yes | Yes |
| Papua New Guinea | 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 | Yes |
| South Sudan | Yes | Yes |
| Sri Lanka | Yes | Yes |
| St. Vincent and the Grenadines | Yes | Yes |
| Sudan | Yes | Yes |
| Suriname | Yes | Yes |
| Swaziland | Yes | Yes |
| Tajikistan | Yes | Yes |
| Tanzania | Yes | Yes |
| Timor-Leste | Yes | Yes |
| Togo | Yes | Yes |
| Tonga | Yes | Yes |
| Turkmenistan | Yes | Yes |
| Tuvalu | Yes | Yes |
| Uganda | Yes | Yes |
| Uzbekistan | Yes | Yes |
| Vanuatu | Yes | Yes |
| Viet Nam | Yes | Yes |
| Yemen | --- | Yes |
| Zambia | Yes | Yes |
| Zimbabwe | Yes | Yes |

# Annex 7. Methodology for estimating the number of patients who have been able to access sofosbuvir and simeprevir (Q4 2013–Q3 2014)

## Sofosbuvir

Global sales figures were obtained from Gilead's quarterly financial statements and filings to the United States Securities and Exchange Commission (forms 10-K and 10-Q) for 2013 and for quarters 1 – 3 of 2014. Sales data are reported in three groups: USA, Europe, and rest of the world.

### *Estimates of number of patients treated with SOF in the USA*

The number of veterans treated with DAAs is available *[137]*. The number of veterans treated with SOF, SIM or both is available for the period 1 January to 25 April 2014 *[182]*. From these numbers, proportions were calculated, which were applied to the entire period of quarters 1 – 3 of 2014 to estimate the number of veterans receiving SOF. The lowest price mentioned by the Veterans Health Administration *[137]* was used to calculate to amount spent by the Veterans Health Administration.

The difference between the latter amount and the USA sales of SOF was calculated and divided by the USA price for 12 weeks of treatment with SOF (US$ 84 000) to estimate the number of people treated with SOF outside the Veterans Health Administration. This was then added to the number treated by the Veterans Health Administration to obtain an estimate for the number of people treated in the USA with SOF.

### *Estimates of number of patients treated with SOF in Europe*

The European sales of SOF were divided by the United Kingdom price of SOF to estimate the number of persons treated with SOF in Europe.

"Early access" sales of Harvoni® (SOF/LDV) in Europe in the third quarter of 2014 were divided by the approximate price negotiated by France for Harvoni® (US$ 60 000) to estimate the number of people who had access to Harvoni®. This number was added to the total number of people with access to SOF in Europe.

### *Estimates of number of patients treated with SOF in the rest of the world*

The rest-of-the-world sales of SOF were divided by the Canadian price of SOF to estimate the number of people treated with SOF in the rest of the world.

Egypt, believed to be the first of the middle-income countries to start treatment with SOF, began registration of patients in the third quarter of 2014. The actual provision of treatment started in mid-October (i.e. in the fourth quarter of 2014).

## Simeprevir

Global sales figures were obtain from Johnson & Johnson's quarterly financial statements and filings to the United States Securities and Exchange Commission (forms 10-K and 10-Q) for 2013 and for quarters 1 – 3 of 2014. Sales data are reported in two groups: USA and rest of the world.

Medivir's sales of SIM were obtained from its interim reports January – June and January – September 2014. These sales were added to the rest-of-the-world sales (Medivir holds the rights to sell SIM in the Nordic countries).

### *Estimates of number of patients treated with SIM in the USA*

The number of veterans treated with DAAs is available *[137]*. The number of veterans treated with SOF, SIM or both is available for the period 1 January to 25 April 2014 *[182]*. From these numbers, proportions were calculated, which were applied to the entire period of quarters 1 – 3 of 2014 to estimate the number

of veterans receiving SIM. The lowest price mentioned by the Veterans Health Administration *[137]* was used to calculate to amount spent by the Veterans Health Administration.

The difference between the latter amount and the USA sales of SIM was calculated and divided by the USA price for 12 weeks of treatment with SIM (US$ 66 360) to estimate the number of people treated with SIM outside the Veterans Health Administration. This was then added to the number treated by the Veterans Health Administration to obtain an estimate for the number of people treated in the USA with SIM.

#### *Estimates of number of patients treated with SIM in Japan*

The number of people treated with SIM in Japan between its launch on 6 December 2013 until the end of the third quarter (30 September) of 2014 is available from the Medicines and Medical Devices Agency, Japan *[183]*.

#### *Estimates of number of patients treated with SIM in the rest of the world*

The price of SIM in Japan is available from Datamonitor Healthcare *[184]*, and was used – together with the number of people treated with SIM – to estimate the amount spent on SIM in Japan. The difference between the estimated spending on SIM in Japan and the reported rest-of-the-world sales of SIM would represent the portion of rest-of-the-world sales outside Japan.

This amount was divided by the United Kingdom price of SIM to estimate the number of people treated with SIM outside Japan and the USA.