UNITAID

2015

HEPATITIS C MEDICINES

Technology and Market Landscape – Update

NOVEMBER 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 Tracy Swan (Treatment Action Group) 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.

World Health Organization

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.

By February 2015, when UNITAID published its *Hepatitis C medicines technology and market landscape*, much had changed in the market for hepatitis C medicines. The role of the two direct-acting antivirals that were first to market had significantly diminished, and both were being discontinued in the USA. Nine new direct-acting antivirals had been launched, though most were only available in a limited number of countries. The February 2015 report took 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where new products have the potential to become "blockbusters" almost overnight – but also risk becoming quickly outdated due to superior products entering the market.

Since February 2015, new clinical data have become available and it is becoming increasingly clear what a simple pan-genotypic regimen for use in all patients – which would be ideal for use in resource-limited settings – may look like. Simultaneously, market data are now available for a wider range of hepatitis C medicines. This short report is published to capture these developments. It updates **only certain sections** of the February 2015 report, as much of the analysis still holds true.

Notably, despite the rapid changes, important challenges (described in the February 2015 report) remain. The new medicines are very expensive; as a result, access is limited even in high-income countries. Access to these new medicines is extremely limited in the rest of the world – with the notable exception of Egypt.

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

AASLD	American Association for the Study of Liver Disease
API	active pharmaceutical ingredient
ART	antiretroviral therapy/treatment
ARV	antiretroviral medicine
DAA	direct-acting antiviral
DCV	daclatasvir
EASL	European Society for the Study of Liver Diseases
FDC	fixed-dose combination
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
LDV	ledipasvir
mg	milligram
Peg-IFN	pegylated interferon
Q	quarter (-year)
r	ritonavir
RBV	ribavirin
SIM	simeprevir
SOF	sofosbuvir
SVR	sustained virological response
US	United States
USA	United States of America
USFDA	United States Food and Drug Administration
WHO	World Health Organization

I. 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.

The *Hepatitis C medicines technology and market landscape*, published in February 2015, surveyed the 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 an important 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.

This current report provides an update of certain sections of the February 2015 report[1] only, as much of the analysis still holds true.

Following a brief description of the methodology, this report updates information on the emerging backbone of HCV treatment – sofosbuvir (SOF) – and on the combination that currently comes closest to the ideal or target profile for an optimally effective and scalable HCV treatment regimen – SOF + daclatasvir (DCV). Section IV updates information on selected market dynamic aspects associated with HCV treatments. Section V updates estimates on the number of people that have been treated with some of the new HCV medicines.

1 This report is available at: http://www.unitaid.eu/images/marketdynamics/publications/HCV_Meds_Landscape_Feb2015.pdf.

II. Methodology

This update 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 of 30 September 2015, unless otherwise indicated.

Technology landscape: Tracy Swan developed the technology landscape material, including the tables and Annex 1. 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, the European Medicines Agency (EMA) 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.

Market landscape: Karin Timmermans developed the market landscape, including the tables, figures and related annexes. 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 with the United States Securities and Exchange Commission), company websites and press releases, and companies' quarterly financial results.

The following reviewers provided valuable input, comments and suggestions on all or part of the document: Isabelle Andrieux-Meyer, Pascale Boulet, Jennifer Cohn, Graciela Diap, Alexandra Grant, Andrew Hill, Fernando Pascual, Françoise Renaud and Stefan Wiktor.

III. Technology landscape

Between late 2013 and December 2014, nine new direct acting antivirals (DAAs) for the treatment of hepatitis C were launched on the global market. Combinations of DAAs are used without interferon and can cure hepatitis C, often in 12 weeks and with limited side-effects. Thus, they revolutionized hepatitis C treatment.

As a result, hepatitis C treatment is evolving rapidly, and the market for DAAs is starting to show some signs of consolidation, as demonstrated by sales figures (see section IV) and treatment guidelines. This report, therefore, updates selected sections of the UNITAID *Hepatitis C medicines technology and market landscape*, published in February 2015.

Recommended regimens

Five treatment regimens are recommended in the treatment guidelines from some of the most prominent associations of hepatologists – the American Association for the Study of Liver Diseases (AASLD) and the European Society for the Study of Liver Disease (EASL) – as well as the Infectious Diseases Society of America (IDSA). These are summarized in Table 1. Meanwhile, the World Health Organization (WHO) HCV Treatment Guidelines are currently being updated.

Table 1. Overview of AASLD/IDSA and EASL recommendations for HCV treatment, by genotype, with approved DAAs[a]

HCV genotype	Currently recommended DAA regimens				
	sofosbuvir + ribavirin	**sofosbuvir/ ledipasvir (FDC)**	**sofosbuvir + simeprevir**	**sofosbuvir + daclatasvir**	**ombitasvir/ paritaprevir/ ritonavir FDC + dasabuvir**
G1	Not recommended	AASLD/IDSA EASL	AASLD/IDSA EASL	AASLD/IDSA EASL	AASLD/IDSA EASL
G2	AASLD/IDSA EASL	Not recommended	Not recommended	AASLD/IDSA EASL	Not recommended
G3	AASLD/IDSA (treatment-naive only) EASL	Not recommended	Not recommended	AASLD/IDSA EASL	Not recommended
G4	AASLD/IDSA	AASLD/IDSA EASL	EASL	EASL	AASLD/IDSA EASL (without dasabuvir)
G5	AASLD/IDSA	AASLD/IDSA EASL	Not recommended	EASL	Not recommended
G6	AASLD/IDSA	AASLD/IDSA EASL	Not recommended	EASL	Not recommended

[a] RBV may be recommended with these regimens.

Sofosbuvir

As can be seen in Table 1, four of the five recommended regimens contain SOF, which is emerging as the backbone of interferon-free treatment of HCV. SOF is safe, potent, once daily, has a high barrier to resistance and limited propensity for drug-drug interactions *[1–8]*. In Australia, Europe and New Zealand, SOF has been approved for use in all six genotypes. SOF-based treatment has been safe and effective, regardless of HIV status, hepatitis C treatment history and stage of liver disease, and before and after liver transplantation *[9–18]*.

SOF has been studied with ribavirin (RBV) and in interferon-free combinations with DAAs from other companies (Achillion, BMS, Janssen, Merck). In clinical trials of SOF-based interferon-free regimens, cure rates are almost always over 90% for patients without cirrhosis, including for those with HIV coinfection. Discontinuation rates for adverse events have been less than 4%, and most common adverse effects were mild (e.g. mild headache, fatigue and weakness) *[9–10,12,14,15,18–21]*. Because of these attributes, SOF currently occupies a central place in interferon-free treatment of HCV.

Cure rates from cohort studies of SOF-based regimens in people that traditionally had low cure rates, such as people with HIV/HCV coinfection, advanced liver disease, a history of treatment failure with pegylated-interferon (Peg-IFN)-based regimens or mild to moderate renal impairment, have been >80% *[22–26]*.

1. Sofosbuvir: resistance and recycling

HCV treatment failure due to baseline or emergent resistance to SOF has been rare in clinical trials *[5,27–28]*. Presence of the S282T or the L159F mutation (associated with SOF resistance) does not always preclude successful re-treatment with a SOF-based regimen in SOF-experienced people, since this resistant virus is less fit than wild-type virus, and tends to disappear rapidly *[5,27–30.]*

It may, therefore, be possible to use SOF in both first-line and second-line regimens. It also appears to be possible to re-treat SOF-experienced people with a SOF-based regimen – although treatment outcome depends on the other DAAs used in the regimen, as well as host and viral factors *[5,27,30–33]*. See Annex 1 for more details.

2. Other NS5B nucleotide polymerase inhibitors?

SOF is the only NS5B nucleotide polymerase inhibitor on the market. Previous attempts to develop DAAs in this class (such as valopicitabine, R-1626, PSI-938 and BMS-986094) have been unsuccessful due to toxicity, lack of efficacy, or both *[1,34]*.

Promising early-stage candidates from this class are in phase I or phase II development (see Table 2). But even if their safety and efficacy are confirmed, it is likely to take several years before these DAAs will be on the market. Moreover, they are likely to be developed and marketed as fixed-dose combinations (FDCs) with other DAAs from the same company (intra-company FDCs).

Table 2. HCV NS5B nucleotide polymerase inhibitors in development *[35–38]*

Compound and company	Type	Status	Comments
AL-516 Janssen	guanosine-based	Preclinical	Toxicity has been a problem with other guanosine-based nucleotides
ACH-3422 Achillion/Janssen	uridine-based	Phase I	700 mg dose
AL-335 Janssen	uridine-based	Phase IIa	Being developed with Janssen DAAs; likely to be co-formulated with them
MK-3682 Merck	uridine-based	Phase II	Being developed with Merck DAAs; likely to be co-formulated with them
VX-135 Vertex	uridine-based	Phase II	After suboptimal results in a phase II trial, Vertex announced plans to out-licence VX-135 in 2014
Mericitabine (RG-7128) Roche	uridine-based	Phase II	Further development is uncertain and may have been stopped due to suboptimal cure rates in clinical trials

Since alternatives to SOF may not be available for some time, companies use SOF as a stand-in for their own early-phase nucleotides. Achillion used SOF (as a proxy for ACH-3422) with ACH-3102 (an NS5A inhibitor) in a 24-person, proof-of-concept "proxy" study; 100% of study participants were cured *[39]*.

Merck's C-SWIFT trial used SOF both as a proxy (for MK-3682), and to shorten treatment by adding it to grazoprevir/elbasvir (a protease and NS5A inhibitor FDC). Although cure rates in the 4- and 6-week arms were suboptimal, 8 weeks of treatment cured 94% (17/18) of people with genotype 1 and cirrhosis. Surprisingly, since grazoprevir and elbasvir had a high failure rate in, and are not being developed for, genotype 3, adding SOF cured 93% (14/15); extending duration to 12 weeks cured 100% (14/14) of people with genotype 3 and 91% (10/12) of people with genotype 3 and cirrhosis *[40,41]*.

Gilead Sciences Inc. (hereinafter Gilead) is looking to shorten treatment by adding RBV or GS-9857 (a protease inhibitor) to SOF and GS-5816 (an NS5A inhibitor). Results have been mixed; and at least 6 weeks of treatment appear to be necessary *[42,43]*.

Sofosbuvir and daclatasvir

Table 1 shows that the European (EASL) HCV treatment guidelines recommend the combination SOF + DCV for use in all HCV genotypes *[44]*. Though other pan-genotypic combinations may be on the horizon, currently the combination SOF + DCV is the leading pan-genotypic DAA regimen.

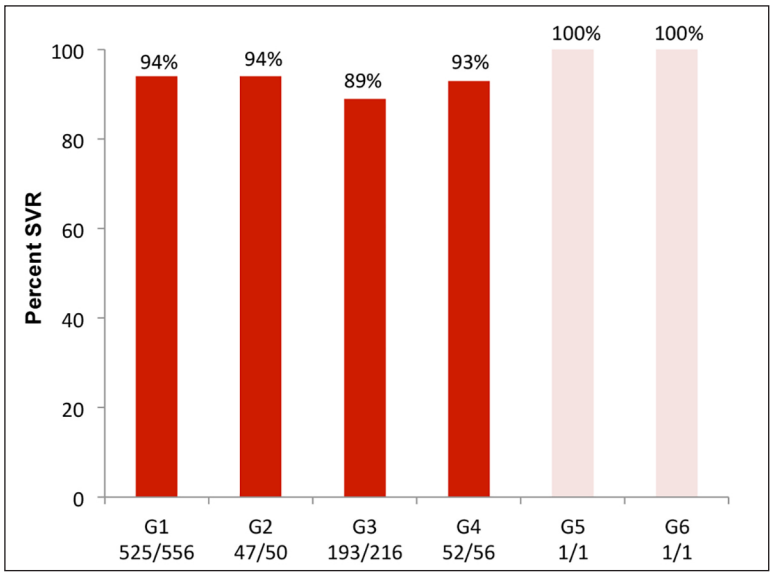
DCV is an NS5A inhibitor. It is safe and well tolerated. Dosing is once a day, and there are no particular food requirements. DCV is the only approved "stand-alone" NS5A inhibitor; the other approved DAAs in this class, ombitasvir and ledipasvir (LDV), are less active against genotypes 2 and 3, and are only available in an FDC *[45–48]*.

Other NS5A inhibitors are being developed by AbbVie, Gilead, Janssen and Merck, but may be developed and marketed only as FDCs with other DAAs from the same company (intra-company FDCs).

Available data show the combination of DCV and SOF (with or without RBV) to be safe, highly effective and tolerable. This appears to be the case in both clinical trials and clinical practice, regardless of HCV treatment history, HIV status or liver disease stage, and before and after liver transplantation *[16,17,19,33,46,49–51]*.

Figure 1 shows the percentage of people cured with SOF + DCV ± RBV (12–24 weeks). It includes data from people with HIV/HCV coinfection, with compensated as well as decompensated cirrhosis, and before as well as after liver transplant.

Figure 1. Sofosbuvir + daclatasvir ± RBV: SVR after 12–24 weeks[a] (%) *[16,17,19,33,52–57]*



[a] Including people with HIV/HCV coinfection, compensated and decompensated cirrhosis, pre- and post-transplant.
Source: Hill A. The minimum cost to cure HCV with DAAs revisited. Presentation at the Second International HIV/Viral Hepatitis Co-Infection Meeting, Vancouver, 17–18 July 2015.

1. HIV/HCV coinfection

Unlike the case of Peg-IFN-based treatment, the cure rates of DAAs in HIV/HCV coinfected people are similar to those in HCV monoinfected patients. Drug-drug interactions between DAAs and ART do limit the HCV treatment options for people living with HIV who are on ART.

Nevertheless, SOF can be used with all WHO-recommended antiretroviral agents (and other antiretroviral medicines [ARVs]) with the exception of tipranavir/r *[8,58]*. DCV can be co-administered with most WHO-recommended ARVs, though it is not recommended for use with nevirapine[2] and dose adjustment is needed when DCV is used with efavirenz or atazanavir/r *[59,60]*.

2. Genotype 3

In the Peg-IFN era, HCV genotypes 2 and 3 were considered "easy to treat" in contrast to HCV genotypes 1 and 4. But when it comes to DAA-based treatment, finding effective regimens for HCV genotype 3 has proven to be a challenge. Options are limited: thus far, in clinical trials, HCV protease inhibitors and non-nucleoside polymerase inhibitors have been less active – or inactive – against genotype 3, leaving only NS5A inhibitors and nucleoside/nucleotide polymerase inhibitors *[61]*.

The phase III ALLY-3 trial underscored the need to optimize treatment for people with genotype 3 and cirrhosis: 12 weeks of SOF and DCV cured over 95% of people without cirrhosis (regardless of treatment experience) versus 58% of treatment-naive people with cirrhosis and 63% of treatment-experienced people with cirrhosis *[33]*.

Treatment outcomes in genotype 3 have been optimized by extending duration of treatment with SOF and DCV, adding RBV, or both, as demonstrated by various cohort studies and compassionate use programmes, where cure rates among people with advanced cirrhosis have reached over 80% (regardless of HIV status or treatment history) *[52–55]*.

2 DCV also is not recommended for use with etravirine.

Ongoing clinical trials are exploring duration of treatment for genotype 3 and cirrhosis. BMS is currently exploring 12 or 16 weeks of SOF, DCV and RBV in people with genotype 3 and cirrhosis in ALLY-3 +, and a single-site trial is exploring 16 or 24 weeks of SOF, DCV and RBV *[62,63]*.

3. Resource-limited settings

The favorable safety profile, efficacy, convenience and simplicity of SOF and DCV make this combination well suited for resource-limited settings. HCV genotyping may no longer be needed, and on-treatment monitoring can be minimized *[64,65]*. Ideally, this once-daily regimen without food requirements would be co-formulated as an FDC to simplify procurement and delivery.

IV. Market landscape

As the technology landscape section in the UNITAID *Hepatitis C medicines technology and market Landscape* (February 2015) and the update above demonstrate, 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 monoinfected 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 provides **an update only of selected aspects of the market** for the breakthrough HCV medicines; it updates information on the regulatory status, sales, licences and availability of generics. It also updates estimates on access to some of the new DAAs.

The market for DAAs is new in all parts of the world and is very limited at present in low- and middle-income countries. As most DAAs have either only recently been approved or are yet to receive regulatory approval, market information is available only for a limited number of countries. As the emerging backbone of HCV treatment, SOF is the primary focus of this section.

Regulatory approval

Boceprevir and telaprevir were approved by the USFDA in May 2011. Simeprevir (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 3 provides an overview of the registration dates of those nine new DAAs as of 30 September 2015, insofar as data are available.

As of October 2015, SOF was registered in one low-income country and eight middle-income countries. Its registration was pending in two low-income countries, five lower-middle-income countries and three upper-middle-income countries, while Gilead reportedly was planning to file for registration in another 11 low- and middle-income countries (see Annex 2).

Table 3. Overview of registration date of new DAAs (as of 30 September 2015)

	simeprevir	sofosbuvir	asunaprevir	daclatasvir	vaniprevir[a]	ledipasvir (FDC with sofosbuvir)	dasabuvir	ombitasvir/ paritaprevir (FDC with ritonavir)
Australia	18 July 2014	30 June 2014	25 May 2015	25 June 2015	--	13 May 2015	10 July 2015	10 July 2015
Brazil	11 Mar 2015	30 Mar 2015		6 Jan 2015	--	--		
Canada	18 Nov 2013	13 Dec 2013	--	13 Aug 2015	--	15 Oct 2014	22 Dec 2014	22 Dec 2014
Chile		Apr 2015			--	--		
Dominican Republic		Apr 2015			--	--		
Egypt		July 2014			--	--		
European Union	14 May 2014	16 Jan 2014	--	22 Aug 2014	--	17 Nov 2014	15 Jan 2015	15 Jan 2015
India		13 Jan 2015			--	--		
Japan	27 Sep 2013	26 Mar 2015	4 July 2014	4 July 2014	26 Sep 2014	3 July 2015	--	28 Sep 2015
Mexico	July 2014	--	--	--	--	--	--	--
Mongolia		Jan 2015			--	May 2015		
New Zealand	--	20 Mar 2014	--	--	--	6 Nov 2014	20 Aug 2015	20 Aug 2015
Pakistan		Feb 2015			--	--		
Republic of Korea		Sep 2015						
Russian Federation	27 Feb 2014	--	3 June 2015	14 July 2015	--	--	21 Apr 2015	21 Apr 2015
Rwanda		Aug 2015			--	Aug 2015		
Saudi Arabia	2014	2014	--	2015	--	2015	2015	2015
Switzerland	4 Mar 2015	18 Mar 2014	--	26 Jun 2015	--	16 Dec 2014	25 Nov 2014	25 Nov 2014
Thailand		Aug 2015		Sep 2015	--	--		
Venezuela (Bolivarian Republic of)		Jan 2015			--	--		
USA	22 Nov 2013	6 Dec 2013	--	24 Jul 2015	--	10 Oct 2014	19 Dec 2014	19 Dec 2014

Notes: -- means the product is not registered as of 30 September 2015. A blank means no information is available. The date of first worldwide registration is underlined.

[a] Merck has announced that vaniprevir will be made available only in Japan *[66]*.

Sales to date

The three DAAs with the largest sales as of 31 December 2014 – SOF, SOF/LDV and SIM – are manufactured and sold by Gilead or Janssen. In 2014, all three were "blockbuster" medicines,[3] and SOF has become a record-breaking new medicine in terms of sales *[67,68]*.

With the exception of SOF, as of 30 September 2015, generic alternatives for these DAAs did not exist or were only recently launched. Sales, therefore, essentially relate to purchases from originator manufacturers. As Tables 4 and 5 and Figure 2 indicate, the sales figures of both SOF and SIM have been impressive since their launch in late 2013. 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.[4] Global sales of SOF/LDV surpassed US$ 9 billion in the first three quarters following its launch (see Table 6).

Table 4. Global originator sales of sofosbuvir (US$ thousands), by quarter-year (Q)

	Q4 2013	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Total
USA	136 364	2 097 791	3 031 507	2 199 519	1 178 000	421 000	615 000	692 000	**10 371 181**
Europe	3 071	163 691	400 218	523 455	459 000	483 000	522 000	337 000	**2 891 435**
Rest of world	--	12 867	48 601	73 119	95 000	68 000	154 000	437 000	**888 587**
Total	**139 435**	**2 274 349**	**3 480 326**	**2 796 093**	**1 732 000**	**972 000**	**1 291 000**	**1 466 000**	**14 151 203**

Source: Gilead Sciences Inc.

Table 5. Global simeprevir sales (US$ thousands), by quarter-year (Q)

	Q4 2013	Q1 2014	Q2 3014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015[a]	Total
USA	13 000	291 000	725 000	671 000	256 000	98 000	50 000	26 000	**2 130 000**
Rest of world	10 000	63 000	109 100	133 900	78 900	140 100	215 600	53 000	**803 600**
Total	**23 000**	**354 000**	**834 100**	**804 900**	**334 900**	**238 100**	**265 600**	**79 000**	**2 933 600**

[a] Data for Q3 2015 do not include Medivir sales.
Sources: Johnson & Johnson; Medivir.

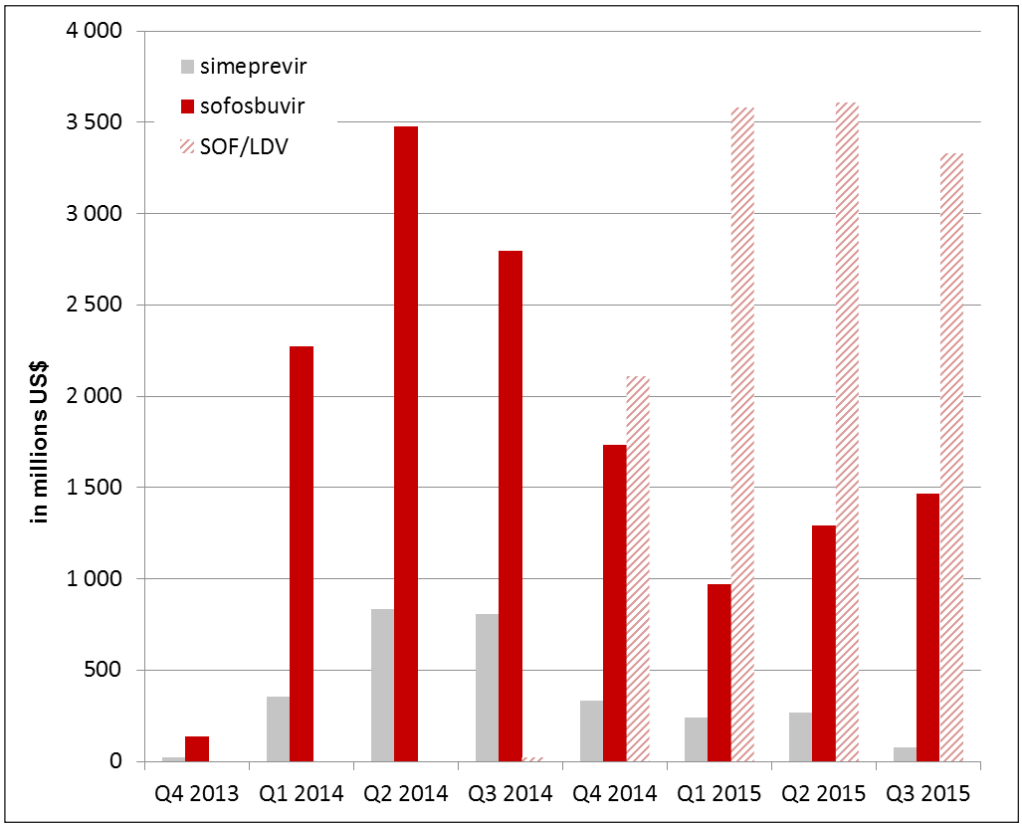
Table 6. Global originator sales of SOF/LDV (US$ thousands), by quarter-year (Q)

	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Total
USA	--	2 001 000	3 016 000	2 826 000	2 541 000	**10 384 000**
Europe	19 966a	83 000	477 000	623 000	532 000	**1 743 966**
Rest of world	--	23 000	86 000	159 000	259 000	**527 000**
Total	**19 966**	**2 107 000**	**3 579 000**	**3 608 000**	**3 332 000**	**12 645 966**

[a] Data refers to "early-access sales" (i.e. before its launch in October 2014) in Europe.
Source: Gilead Sciences Inc.

3 "A 'blockbuster medicine' is defined as being one that achieves annual global revenues of over US$ 1 billion" *[69]*.
4 Though approved in September, SIM was launched in Japan only on 6 December 2013.

Figure 2. Global sales of SOF,[a] SIM and SOF/LDV[a] (US$ millions), Q4 2013–Q3 2015



[a] Originator sales only.
Sources of data: Gilead Sciences Inc.; Johnson & Johnson; Medivir.

Sales of the other DAAs that were launched in 2014 are summarized in Table 7 and Figure 3, with the exception of vaniprevir, for which data are not available.[5]

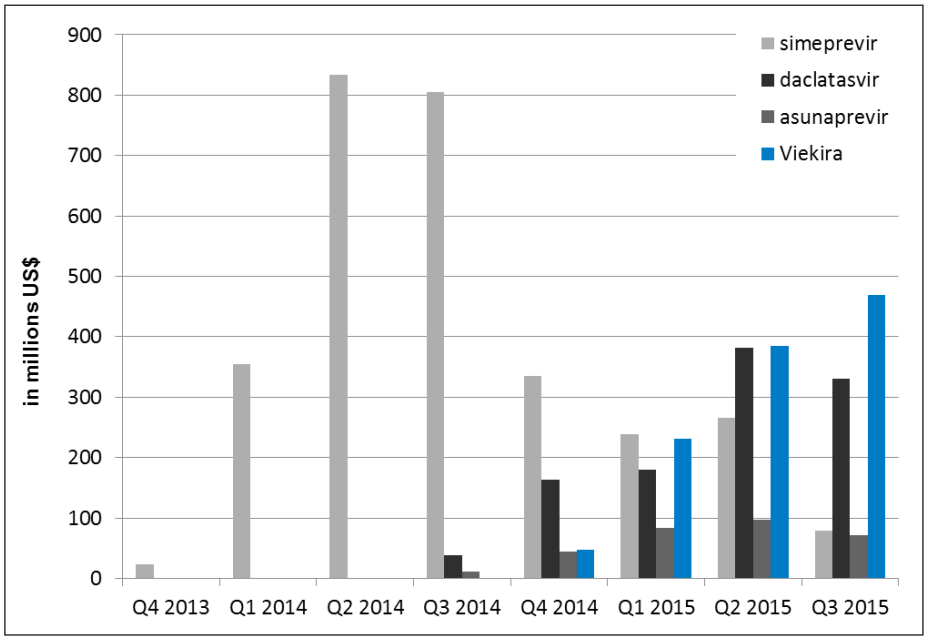
Table 7. Global sales of other DAAs (US$ thousands), by quarter-year (Q)[a]

Product	Region	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Total
asunaprevir	USA	--	--	--	--	--	**308 000**
	ROW	11 000	44 000	84 000	97 000	72 000	
daclatasvir	USA	--	--	--	--	111 000	**1 093 000**
	ROW	38 000	163 000	180 000	382 000[b]	219 000	
Viekira	USA	--	48 000	138 000	227 000	242 000	**1 133 000**
	ROW	--	--	93 000	158 000	227 000	

ROW, rest of the world
[a] Merck has announced that vaniprevir will be made available only in Japan *[66]*; sales data are not available.
[b] This figure includes $170 million in previously deferred revenue in France.
Sources: AbbVie; Bristol-Myers Squibb.

5 Merck has announced that vaniprevir will be made available only in Japan *[66]*.

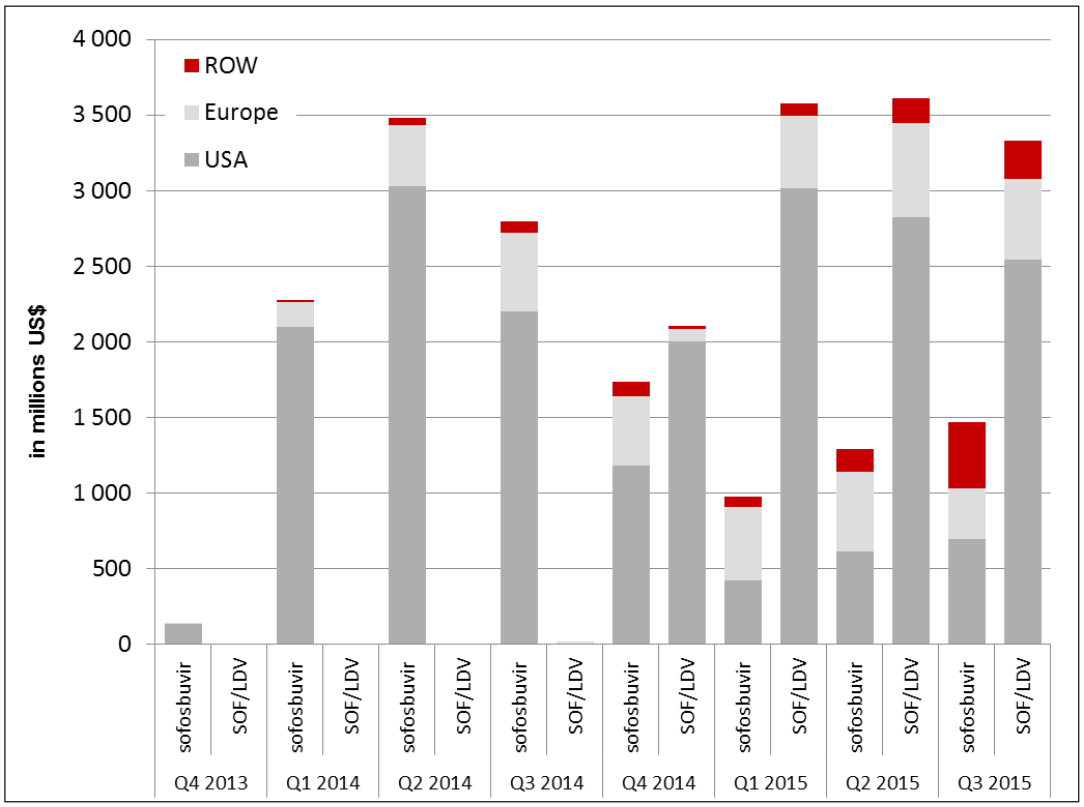
Figure 3. Global sales of asunaprevir, DCV, SIM and Viekira (US$ millions), Q3 2014–Q3 2015



Sources of data: AbbVie; Bristol-Myers Squibb; Johnson & Johnson; Medivir.

However, high-income countries account for nearly all sales of the new DAAs, with limited penetration in low- and middle-income countries. Since their launch, originator sales of SOF and SOF/LDV in the United States of America (USA) and Europe accounted for more than 94% of their respective worldwide sales (Figure 4).

Figure 4. Global sales of SOF and SOF/LDV by geographical region[a] (US$ millions), Q4 2013–Q3 2015



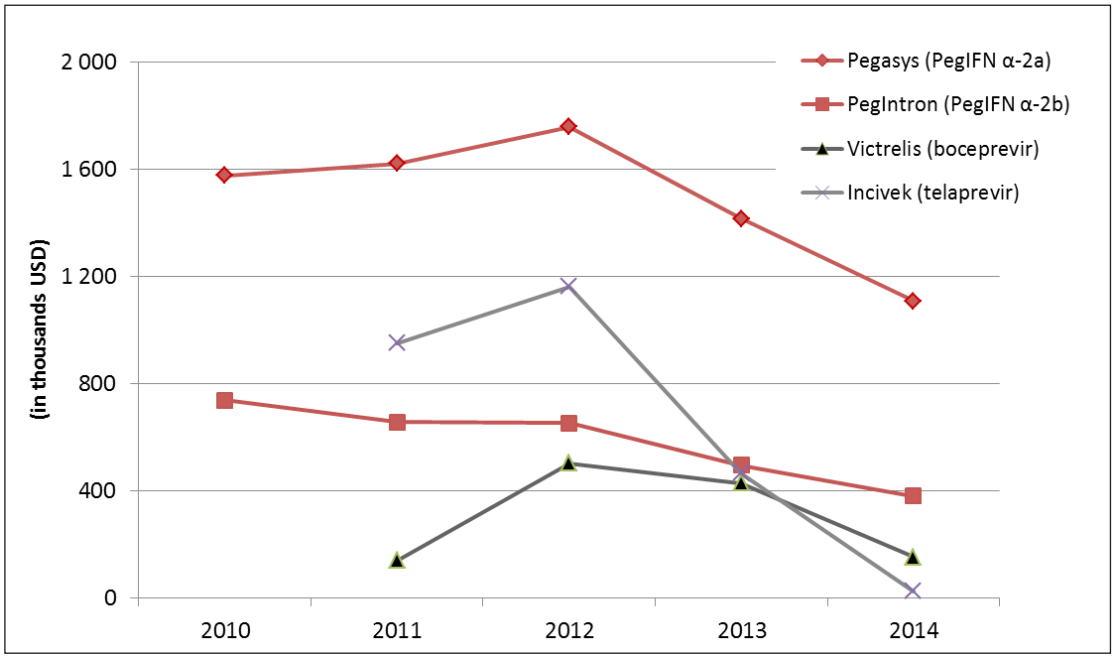
ROW, rest of world
[a] Originator sales only.
Sources of data: Gilead Sciences Inc.; Johnson & Johnson; Medivir.

The emergence of highly effective DAAs has resulted in a substantial expansion of the global market for HCV medicines. Together, the new DAAs accounted for US$ 15 billion in global sales in 2014 – three times the total market value of HCV drugs in 2012, which amounted to around US$ 5 billion (Peg-IFN and RBV together represented US$ 3.5 billion in purchases in 2012, with boceprevir and telaprevir accounting for the remainder).[6] Predictably, the older HCV medicines have lost market share (Figure 5).

Vertex announced in August 2014 that it would stop marketing telaprevir in the USA "in view of available alternative treatments and the diminishing market demand" *[70]*. 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 *[71]*.

6 Merck, Roche and Vertex 10K reports.

Figure 5. Global sales of Peg-IFN, boceprevir and telaprevir (US$ thousands), 2010–2014



Notes: Pegasys sales have been converted from Swiss francs (CHF) using average annual exchange rates (OANDA). Boceprevir and telaprevir received marketing approval in May 2011.
Sources of data: Merck; Roche; Vertex.

Patents and licences

Annex 3 provides an overview of the patent status of the nine new DAAs, insofar as known.

Starting in September 2014, Gilead signed voluntary licences with a growing number of generic producers. As licence-holders, these companies have the right to manufacture generic versions of SOF, LDV and – once approved – velpatasvir (GS-5816). The licence, which is publicly available, initially allowed supply of generic versions to 91 low- and middle-income countries *[72]*. Since then, 10 additional countries have been included in the licence (see Annex 4 for the list of countries) *[73]*.

The countries included in the licences will be able to buy generic versions of SOF, LDV and velpatasvir (GS-5816) 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 (non-licence-holding) generic manufacturers (see Annex 5 for a list of generic DAAs).

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 3) – a compulsory licence would have to be issued on those pending patents in the concerned country and/or in India. However, national patent laws may not 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.[7] Since some patents related to SOF reportedly have been granted in India *[72]* and several other patent applications are currently pending there *[74]*, India may have to issue compulsory licences to enable licence-holders to supply. It remains to be seen how well this would work in practice.

7 This is because of requirements in the Gilead licence.

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. Or countries could opt for local production, provided they can find a source of the active pharmaceutical ingredient (API)[8] or are able to produce the API locally.

Table 8 summarizes the options for obtaining generic versions of SOF and SOF/LDV.

Table 8. Overview of options for supply of generic sofosbuvir and SOF/LDV

Country	Patent situation	Options for supply of generics
Country included in Gilead's licence	Patents	■ Import from Gilead licencees
	Patent applications pending	■ Import from Gilead licencees ■ Import from non-licence-holding generic manufacturers, depending on national law
	No patents	■ Import from Gilead licencees ■ Import from non-licence-holding generic manufacturers ■ Local production
Country not included in Gilead's licence	Patents	– Generic supply not allowed
	Patent applications pending	■ Import from Gilead licencees possible if compulsory licence issued in the country or in India[a] ■ Import from non-licence-holding generic manufacturers, depending on national law
	Patents (or patent applications) and compulsory licence	■ Import from Gilead licencees ■ Import from non-licence-holding generic manufacturers ■ Local production
	No patents	■ Import from Gilead licencees possible if compulsory licence issued in India[a] ■ Import from non-licence-holding generic manufacturers ■ Local production

[a] A compulsory licence in India would be required because Gilead's licence authorizes licencees (licence-holding generic manufacturers) to produce *only* for sale in countries inside the territory of the licence. Outside the territory, the Gilead licence requests a compulsory licence to be issued in India and/or the country concerned, in order for licencees to be allowed to supply.

Bristol-Myers Squibb announced its intention to issue voluntary licences for DCV in November 2014; however, no licence has been issued as of 31 October 2015. AbbVie and Janssen have not announced plans regarding licensing of their DAAs.

Generic versions

Several manufacturers in India have started to market generic versions of SOF; at least 11 generics are on the market in India. In addition, manufacturers in countries where there are no blocking patents on SOF have started to market generic versions of SOF, thus, there are reportedly several generics on the market in Bangladesh and Egypt[9] (see Annex 5 for details).

The generic versions of SOF listed in Annex 5 have been registered by the relevant national regulatory authority. None has as yet received WHO prequalification, though it is understood that at least one product is currently in the process of WHO prequalification.

8 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 that hold a licence.

9 Generic versions of SOF are being developed in other countries as well, for example, in Morocco *[75]*.

The first generic version of SOF/LDV was launched in Nepal on 28 October 2015 by Natco Pharma Ltd *[76,77]*, others are reportedly under development in India *[78,79]*.

Two generic versions of DCV are registered in Bangladesh (see Annex 5), and Indian companies are reportedly developing generic DCV, as well as FDCs of SOF with DCV *[80]*.

Demand

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 applied for access to this drug through an internet-based application *[81]*. By the end of October 2015, this number had reportedly surpassed 1 million *[82]*.

In many other countries, demand and uptake are limited, among others, by a lack of awareness about HCV, a lack of affordable and reliable tools for screening and diagnosing HCV at the point-of-care and the absence of HCV programmes.

Market shortcomings

As the discussion above indicates, generic DAAs are starting to become available, potentially offering opportunities to roll out these breakthrough therapies in low- and middle-income countries. Nevertheless, many of the market shortcomings identified in the *Hepatitis C medicines technology and market landscape* (February 2015) have yet to be addressed or resolved; these include, among others, the lack of access to diagnosis (which limits demand), the fact that the new DAAs have not yet been registered or launched in most low- and middle income countries, the lack of normative guidance and health system capacity at the national level, the absence of HCV programmes and the lack of funding for HCV treatment.

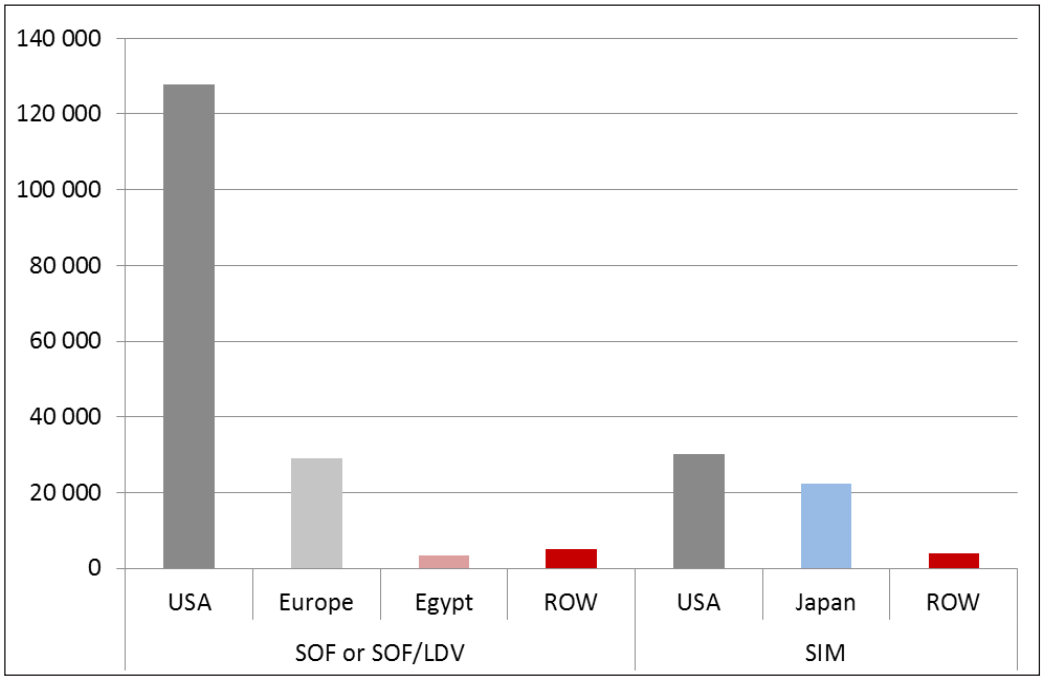
As long as these market shortcomings remain, the volume of DAAs that would be required to enable generic prices to go down is unlikely to materialize in resource-limited settings. As a result, the vicious circle of low volumes and high prices, described in the *Hepatitis C medicines technology and market landscape* (February 2015), still persists.

V. Access estimates

On the basis of the sales data, prices and registration data described above, it is possible to estimate the number of people who have had access to the top three best-selling DAAs in 2014. Worldwide, around 56 000 people have been treated with SIM and around 140 000 have been treated with SOF between the launch of these products in Q4 2013 and 31 December 2014. In addition, around 25 000 people would have had access to SOF/LDV in 2014. The geographical distribution of people who have been treated with SOF, SOF/LDV or SIM (see estimates in Figure 6) shows that there has been minimal access to these drugs outside Europe, Japan and the USA.

It may be noted that 2014 sales of SOF, SOF/LDV and SIM in the rest of the world (indicated by "ROW" in Figure 6) refer mostly to high-income countries, where these medicines were registered (Table 3)[10].

Figure 6. Estimated number of people treated with SOF, SOF/LDV or SIM by region (Q4 2013–Q4 2014)

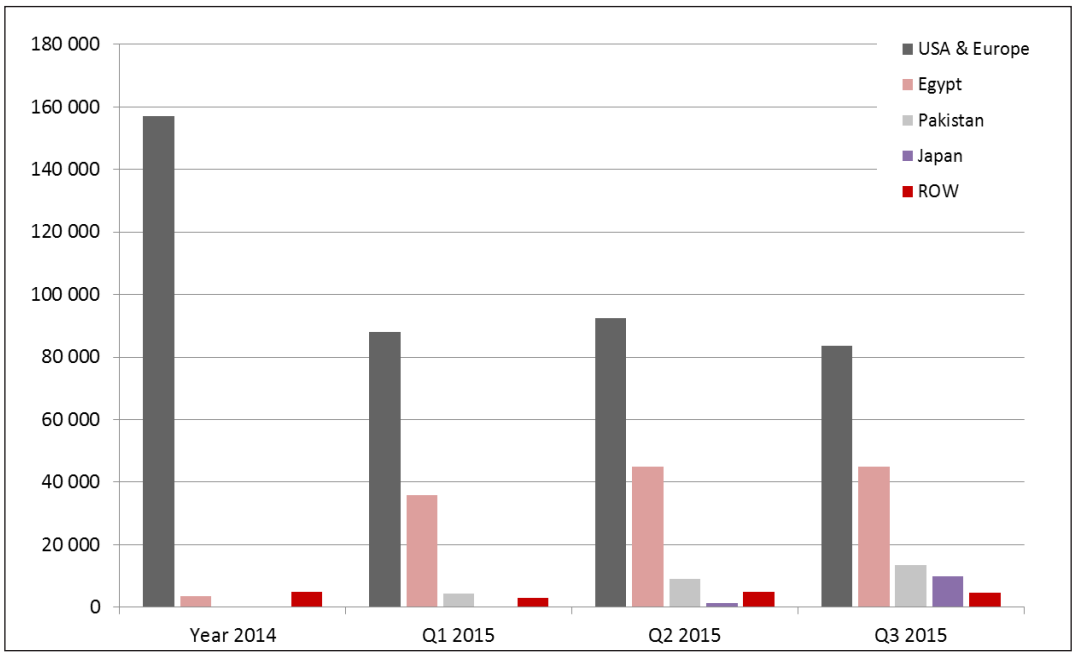


ROW, rest of world
Note: Sales of SOF and SIM in Q4 2013 represent less than 1.5% of their total sales over the period Q4 2014–Q4 2014.
See Annex 6 for sources and methodology used to prepare these estimates.

Similarly, it is estimated that in the first half of 2015, approximately 284 000 people worldwide have had access to SOF or SOF/LDV sold by originator companies. The majority of these (around 180 000 people) were in Europe or the USA. In addition, it is estimated that around 80 000 people in Egypt and 13 500 people in Pakistan have had access to these medicines in the first six months of 2015 – as well as around 8000 people elsewhere in the world (see Figure 7).

10 Exceptions are Mexico, where SIM was registered in July 2014, and Egypt, where SOF was registered in July 2014. Estimates for Egypt are depicted separately in Figure 6. Note that the actual distribution of SOF in Egypt only began in mid-October 2104 *[83]*.

Figure 7. Estimated number of people treated with SOF or SOF/LDV by region[a] (2014 and Q1–Q3, 2015)



ROW, rest of world
[a] Based on originator sales only.
See Annex 6 for sources and methodology used to prepare these estimates.

In the first three quarters of 2015, the number of people worldwide who have been able to access treatment with SOF or SOF/LDV sold by originator companies is estimated to be approximately 440 000. About 60% of them live in Europe or the USA, and almost 29% in Egypt.

Outside Egypt, Europe, Japan, Pakistan and the USA, access to SOF or SOF/LDV sold by originator companies – though harder to estimate due to the very significant variation in prices – is unlikely to have reached 5% of the total number of people treated with either of these medicines.

ANNEXES

Annex 1. Summary of sofosbuvir re-treatment trials and results

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

Sources: [29–33,84].

Annex 2. Overview of the registration status of sofosbuvir in developing countries as of October 2015

	Low-income countries	Lower-middle-income countries	Upper-middle-income countries
Registered	Rwanda	Egypt India Pakistan Philippines	Brazil Dominican Republic Mongolia Thailand
Registration pending (application filed)	Uganda United Republic of Tanzania	Bolivia (Plurinational State of) El Salvador Indonesia Kenya Nigeria	Colombia Mexico South Africa
Registration planned or registration file under preparation	Haiti Mozambique	Cameroon Guatemala Indonesia Myanmar Uzbekistan Viet Nam	Ecuador Peru Tunisia

Sources: Sovaldi® registration in the developing world. Foster City CA: Gilead Sciences Inc.; October 2015 (http://www.gilead.com/~/media/files/pdfs/other/sovaldi%20registration%20-%20ocotber%202015.pdf, accessed on 11 November 2015); List of economies. Washington DC: World Bank; July 2015.

Annex 3. Summary of patent information of selected DAAs in low- and middle-income countries, based on available data

	Argentina	ARIPO	Brazil	Chile	China	Colombia	Costa Rica	EAPO	Ecuador	Egypt	Ethiopia	Georgia	India	Indonesia	Iran (Islamic Republic of)	Jordan	Lebanon	Malaysia	Mexico	Morocco	Nigeria	OAPI	Pakistan	Peru	Philippines	South Africa	Thailand	Tunisia	Ukraine	Uruguay	Venezuela (Bolivarian Republic of)	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	G	•	G	F	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	--	Viekira Pak™
	F	•	F	•	G	F	•	G	•	F	•	•	F	•	•	•	•	•	F	•	•	•	•	F	F	G	F	•	•	F	•	F	
paritaprevir	G	•	F	•	F	•	•	•	•	•	•	•	F	•	•	•	•	•	F	•	•	•	•	F	•	G	•	•	•	F	•	•	
ombitasvir	F	•	•	•	F	F	•	F	F	•	•	•	F	•	•	•	•	•	F	•	•	•	•	F	•	G	•	•	G	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 *[72]*

= included in voluntary licences = voluntary licence announced

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

Notes: For each molecule, the first row relates to the primary patent; the second row combines information for all other identified patents (except SOF, 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).

Source of data: WHO *[74,85–90]*.

Annex 4. Overview of countries and territories included in voluntary licences

Country	SOF, LDV, GS-5816 (Gilead)	DCV (Bristol-Myers Squibb)
Afghanistan	Yes	Yes
Algeria	Yes	Yes
Angola	Yes	Yes
Antigua and Barbuda	Yes	---
Azerbaijan	---	Yes
Bangladesh	Yes	Yes
Belize	---	Yes
Benin	Yes	Yes
Bhutan	Yes	Yes
Bolivia (Plurinational State of)	Yes	Yes
Botswana	Yes	Yes
Burkina Faso	Yes	Yes
Burundi	Yes	Yes
Cambodia	Yes	Yes
Cameroon	Yes	Yes
Cape Verde	Yes	Yes
Central African Republic	Yes	Yes
Chad	Yes	Yes
Comoros	Yes	Yes
Congo (Republic of the)	Yes	Yes
Cook Islands	Yes	Yes
Costa Rica	---	Yes
Côte d'Ivoire	Yes	Yes
Cuba	Yes	Yes
Democratic People's Republic of Korea	Yes	Yes
Democratic Republic of the Congo	Yes	Yes
Djibouti	Yes	Yes
Dominica	Yes	Yes
Dominican Republic	---	Yes
Ecuador	---	Yes
Egypt	Yes	---
El Salvador	Yes	Yes
Equatorial Guinea	Yes	Yes
Eritrea	Yes	Yes
Ethiopia	Yes	Yes

Country	SOF, LDV, GS-5816 (Gilead	DCV (Bristol-Myers Squibb)
Fiji	Yes	Yes
Gabon	Yes	Yes
Gambia	Yes	Yes
Georgia	---	Yes
Ghana	Yes	Yes
Grenada	---	Yes
Guatemala	Yes	Yes
Guinea	Yes	Yes
Guinea-Bissau	Yes	Yes
Guyana	Yes	Yes
Haiti	Yes	Yes
Honduras	Yes	Yes
India	Yes	Yes
Indonesia	Yes	Yes
Iraq	---	Yes
Jamaica	---	Yes
Kenya	Yes	Yes
Kiribati	Yes	Yes
Kyrgyzstan	Yes	---
Lao People's Democratic Republic	Yes	Yes
Lesotho	Yes	Yes
Liberia	Yes	Yes
Libya	Yes	Yes
Madagascar	Yes	Yes
Malawi	Yes	Yes
Maldives	Yes	Yes
Mail	Yes	Yes
Marshall Islands	Yes	Yes
Mauritania	Yes	Yes
Mauritius	Yes	Yes
Micronesia (Federated States of)	Yes	Yes
Mongolia	Yes	Yes
Morocco	Yes	Yes
Mozambique	Yes	Yes
Myanmar	Yes	Yes
Namibia	Yes	Yes

(continues)

Country	SOF, LDV, GS-5816 (Gilead)	DCV (Bristol-Myers Squibb)
Nauru	Yes	Yes
Nepal	Yes	Yes
Nicaragua	Yes	Yes
Niger	Yes	Yes
Nigeria	Yes	Yes
Niue	---	Yes
Pakistan	Yes	Yes
Palau	Yes	Yes
Panama	---	Yes
Papua New Guinea	Yes	Yes
Paraguay	Yes	Yes
Philippines	Yes	Yes
Rwanda	Yes	Yes
Saint Lucia	---	Yes
Saint Vincent and the Grenadines	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

Country	SOF, LDV, GS-5816 (Gilead)	DCV (Bristol-Myers Squibb)
South Sudan	Yes	Yes
Sri Lanka	Yes	Yes
Sudan	Yes	Yes
Suriname	Yes	Yes
Swaziland	Yes	Yes
Syria	---	Yes
Tajikistan	Yes	---
Timor-Leste	Yes	Yes
Togo	Yes	Yes
Tonga	Yes	Yes
Tunisia	Yes	Yes
Turkmenistan	Yes	Yes
Tuvalu	Yes	Yes
Uganda	Yes	Yes
United Republic of Tanzania	Yes	Yes
Uzbekistan	Yes	Yes
Vanuatu	Yes	Yes
Viet Nam	Yes	Yes
West Bank and Gaza Strip	---	Yes
Yemen	---	Yes
Zambia	Yes	Yes
Zimbabwe	Yes	Yes

Notes: Text in red colour reflects changes from the initial Gilead voluntary licence or from the initial list of countries that Bristol-Myers Squibb intends to include in its voluntary licence [73,109].
--- means the country is not included in the licence.

Annex 5. Overview of generic versions of DAAs

This annex provides an overview of generic versions of different DAAs known to be on the market in selected countries. Unless otherwise indicated, the products listed in this annex are registered by the relevant national regulatory authority.[11] This is not intended to be an exhaustive list.

Generic versions of daclatasvir[a]

Product name/brand name	Market authorization holder/supplier	Voluntary licence from BMS[12]
Bangladesh		
Daclacee 60	RAK Pharmaceuticals Ltd	No
Daclavir	Beacon Pharmaceuticals Ltd	No

[a] *Source (columns 1 and 2)*: Drug Administration Bangladesh, 1 November 2015. In as far as known, both products were launched in the first half of October 2015.

Generic versions of sofosbuvir[a]

Product name/brand name	Market authorization holder/supplier	Voluntary licence from Gilead
Bangladesh		
Hepacare 400 mg	Healthcare Pharmaceuticals Ltd	No
Hepcee	RAK Pharmaceuticals Ltd	No
Hopetavir	Incepta Pharmaceuticals Ltd	No
Soforal	Beacon Pharmaceuticals Ltd	No
Sofovir C	Beximco Pharmaceuticals Ltd	No
Egypt		
Sovaldi[b]	IBIS Pharma	Distributor for Gilead in Egypt
Augispov	AUG Pharma	No
Grateziano	European Egyptian Pharmaceutical Industries	No
Gratisovir	Pharco	No
Heterosofit	Pharmed Health Care-Egypt	Yes, for Egypt only
Hoforhep	Global NAPI Pharmaceuticals (GNP)	No
Mpiviropack	Marcyrl Pharmaceutical Industries	No
Serinosprevir	Innovative Pharma	No
Sofolanork	Mash Company For Pharmaceutical Industries	No
Sofosbuvir-Biomed	Biomed pharmaceuticals	No
Sofosbuvir I.P.M.C	Innova Pharmaceutical Manufacturing Company	No
sofosbuvir-pharco b international	Pharco B International-Egpyt	No
Sofovirotal	Future Pharmaceutical Industries-Egypt	No
Tigaglor	Asia Mary Company	No

11 The mention of specific products or companies does not imply that they are endorsed or recommended.
12 Insofar as known, BMS has not signed any licences for DCV.

India		
Sovaldi[b]	Mylan Pharmaceuticals Ltd	Distributor for Gilead in India
Cimivir	Biocon	Yes
Hepcinat	Natco Pharma Ltd	Yes
Hepcvir	Cipla Ltd	Yes
MyHep	Mylan Pharmaceuticals Ltd	Yes
Resof	Dr Reddy's Laboratories	No
Sofab	Ranbaxy Laboratories	Yes
Sofovir	Hetero Healthcare Ltd	Yes
SoviHep	Zydus Heptiza (Zydus Cadila)	Yes
Spegra	Emcure Pharmaceuticals Ltd	No
Viroclear	Abbott India Ltd	No
Virso	Strides Arcolab Ltd	Yes

[a] *Sources:* Drug Administration Bangladesh, 1 November 2015; Egyptian Drug Agency, 1 November 2015; Gilead Sciences Inc. *[73]*; TREAT Asia/amfAR – The foundation for AIDS Research *[91]*.
[b] Originator product.

Generic versions of SOF/LDV[a]

Product name/brand name	Market authorization holder/supplier	Voluntary licence from Gilead
Bangladesh[13]		
Lesovir C	Beximco Pharmaceuticals Ltd	No
Twinvir	Incepta Pharmaceuticals Ltd	No
India/Nepal[14]		
Hepcinat LP[14]	Natco Pharma Ltd	Yes

[a] *Sources:* Drug Administration Bangladesh, 1 November 2015; Gilead Sciences Inc. *[73]*.

13 In as far as known, both products were launched in early September 2015 *[92]*.
14 Launched in Nepal on 28 October 2015 [76,77]. As of 1 November 2015, there were no reports that the product has already been registered or launched in India.

Annex 6. Methodology for estimating the number of patients treated with sofosbuvir, SOF/LDV or simeprevir

Estimates for Q4 2014

SOF

Estimates of the number of patients treated with SOF in Europe and the USA

The numbers of people who received SOF in Europe and the USA in Q4 2014 was estimated using the same methodology as the estimates for Q4 2013–Q3 2014 (see the UNITAID *Hepatitis C medicines technology and market landscape*, February 2015, Annex 7).

Estimates of the number of patients treated with SOF in Egypt

Egypt, believed to be the first middle-income country to start treatment with SOF, began providing treatment mid-October 2014. The number of patients receiving treatment in the first 6 weeks is available *[83]*. The number of patients for the rest of Q4 2014 was estimated by extrapolation.

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

The price of SOF in Egypt is known to be US$ 900 for 12 weeks treatment. This price was used – together with the estimated number of people treated with SOF – to estimate the amount spent on SOF in Egypt.

The difference between the estimated spending on SOF in Egypt and the reported rest-of-the-world sales of SOF would represent the portion of rest-of-the-world sales outside Egypt. This amount was divided by the Canadian price of SOF to estimate the number of people treated with SOF outside Egypt, Europe and the USA.

SIM

Estimates of the 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 Q3 of 2014 is available from the Medicines and Medical Devices Agency, Japan *[93]*.

The number of people treated with SIM in Japan in Q4 2014 was estimated by extrapolation from the above number and subsequent reduction of the extrapolated number by 40%, to take into account the 40% reduction in rest-of-the-world sales.

Estimates of the number of patients treated with SIM in the USA and the rest of the world

The number of people who received SIM in the USA and the rest of the world (outside Japan) in Q4 2014 was estimated using the same methodology as the estimates for Q4 2013–Q3 2014 (see the UNITAID *Hepatitis C medicines technology and market landscape*, February 2015, Annex 7).

SOF/LDV

Estimates of the number of patients treated with SOF/LDV in the USA

The calculations on the use of SOF (see above and the UNITAID *Hepatitis C medicines technology and market landscape*, February 2015, Annex 7) indicated the percentage of SOF used by the Veterans Health Administration versus total use of SOF in the USA. It was assumed that the same ratio would apply to the relative use of SOF/LDV by the Veterans Health Administration (versus total use of SOF/LDV in the USA). The price reportedly paid for SOF/LDV by the Veterans Health Administration (US$ 69 636) *[94]* was used to calculate the amount spent on SOF/LDV by the Veterans Health Administration.

The difference between the latter amount and the USA sales of SOF/LDV was calculated and divided by the USA price for 12 weeks of treatment with SOF/LDV (US$ 94 500) to estimate the number of people treated with SOF/LDV outside the Veterans Health Administration. This number was adjusted to account for the lower prices due to competition from the AbbVie regimen starting late December 2014. The adjusted number 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/LDV.

Estimates of the number of patients treated with SOF/LDV in Europe

The European sales of SOF/LDC were divided by the Italian price of SOF/LDV (approximately US$ 51 000) *[95]* to estimate the number of people treated with SOF/LDV in Europe.

Estimates of the number of patients treated with SOF/LDV in the rest of the world

The rest of the world sales of SOF/LDC were divided by the price of SOF/LDV in New Zealand (US$ 57 000) *[96]* to estimate the number of people treated with SOF/LDV in the rest of the world.

Estimates for Q1–Q3 2015

SOF

Global sales figures were obtained from Gilead's quarterly financial statements and filings with the United States Securities and Exchange Commission (forms 10-Q) for 2015. Sales data are reported in three groups: USA, Europe, and rest of the world.

Estimates of the number of patients treated with SOF in Europe and the USA

The listed price of SOF in the USA is US$ 84 000/12 weeks. Based on reported discounts *[97]*, it was assumed that the actual price is US$ 45 360/12 weeks. The USA sales of SOF were divided by this price to estimate the number of people treated with SOF in the USA.

The European sales of SOF were divided by the French price of SOF (approximately US$ 46 500) *[95]* to estimate the number of people treated with SOF in Europe.

These two estimates were added up to obtain an estimate for the total number of people with access to SOF in Europe plus the USA.

The estimates for SOF and SOF/LDV (see below) in Europe and the USA were added up; the estimated totals were in line with the totals reported by Gilead *[98,100,101]*.

Estimates of the number of patients treated with SOF in Egypt

The estimates for Egypt are based on the number of people treated with SOF as reported by officials from Egypt at the World Hepatitis Summit and at other meetings. These estimates are broadly in line with the numbers reported by Gilead *[99–101]*.

Estimates of the number of patients treated with SOF in Pakistan

The number of people receiving SOF in Pakistan was estimated based on available reports *[99–102]*. These are private sector sales only.

Estimates of the number of patients treated with SOF in Japan

SOF was launched in Japan on 25 May 2015 *[100]*. The price of SOF in Japan is reportedly around US$ 43 000 for 12 weeks treatment *[103–105]*. Sales of SOF in Japan amounted to US$ 62 million in Q2 *[100]* and US$ 343 million in Q3 *[101]*. These sales were divided by the price to estimate the number of people treated with SOF in Japan.

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

The price of SOF in Egypt is known to be US$ 900 for 12 weeks treatment. This price was used – together with the estimated number of people treated with SOF – to estimate the amount spent on SOF in Egypt.

The private sector price of SOF in Pakistan, and the evolvement of that price, was estimated based on available reports *[102,106]*. This was used – together with the estimated number of people treated with SOF – to estimate the amount spent on SOF in Pakistan.

The difference between, on the one hand, the sales in Japan and the estimated spending on SOF in Egypt plus Pakistan and, on the other hand, the reported rest-of-the-world sales of SOF would represent the portion of rest-of-the-world sales outside Egypt, Japan and Pakistan.

This amount was divided by US$ 20 000 (roughly the average between the price for 12 weeks treatment reported for Canada (approximately US$ 41 500) *[107]* and in India (US$ 900) to estimate the number of people treated with SOF outside Egypt, Europe, Japan, Pakistan and the USA.

SOF/LDV

Global sales figures were obtained from Gilead's quarterly financial statements and filings with the United States Securities and Exchange Commission (forms 10-Q) for 2015. Sales data are reported in three groups: USA, Europe, and rest of the world.

Estimates of the number of patients treated with SOF/LDV in Europe and the USA

The listed price of SOF/LDV in the USA is US$ 94 500/12 weeks. Based on reported discounts *[97]*, it was assumed that the actual price is US$ 51 030/12 weeks. The USA sales of SOF/LDV were divided by this price to estimate the number of people treated with SOF/LDV in the USA.

The European sales of SOF/LDV were divided by the Italian price of SOF/LDV (approximately US$ 51 000) *[95]* to estimate the number of people treated with SOF in Europe.

These two estimates were added up to obtain an estimate for the total number of people with access to SOF/LDV in Europe plus the USA.

The estimates for SOF and SOF/LDV in Europe and the USA were added up; the estimated totals were in line with the totals reported by Gilead *[98,100,101]*.

Estimates of the number of patients treated with SOF/LDV in Japan

SOF/LDV was launched in Japan on 1 September 2015 *[101]*. The price of SOF/LDV in Japan is reportedly around US$ 56 000 for 12 weeks treatment *[108]*. Sales of SOF in Japan amounted to US$ 111 million in Q3 *[101]*. These sales were divided by the price to estimate the number of people treated with SOF in Japan.

Estimates of the number of patients treated with SOF/LDV in the rest of the world

The difference between the sales in Japan and the reported rest-of-the-world sales of SOF/LDV would represent the portion of rest-of-the-world sales outside Japan.

This amount was divided by the price of SOF/LDV in New Zealand (approximately US$ 57 000) *[96]* to estimate the number of people treated with SOF/LDV outside Europe, Japan and the USA.

References

1. Bourlière M, Oules V, Ansaldi C, Adhoute X, Castellani P. Sofosbuvir as backbone of interferon free treatments. Dig Liver Dis. 2014;46(Suppl. 5):S212–S220. doi:10.1016/j.dld.2014.09.024.

2. Feld JJ. Interferon-free strategies with a nucleoside/nucleotide analogue. Semin Liver Dis. 2014;34(1):37–46. doi:10.1055/s-0034-1371009.

3. Gentile I, Borgia F, Buonomo AR, Castaldo G, Borgia G. A novel promising therapeutic option against hepatitis C virus: an oral nucleotide NS5B polymerase inhibitor sofosbuvir. Curr Med Chem. 2013;20(30):3733–42.

4. Kumar S, Jacobson IM. Antiviral therapy with nucleotide polymerase inhibitors for chronic hepatitis C. J Hepatol. 2014;61(Suppl. 1):S91–S97. doi:10.1016/j.jhep.2014.09.006.

5. Noell BC, Besur SV, deLemos AS. Changing the face of hepatitis C management: the design and development of sofosbuvir. Drug Des Devel Ther. 2015;9:2367–74. doi:10.2147/DDDT.S65255.

6. Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. Liver Int. 2014;34(Suppl. 1):69–78. doi:10.1111/liv.12423.

7. Sofia MJ. Beyond sofosbuvir: What opportunity exists for a better nucleoside/nucleotide to treat hepatitis C? Antiviral Res. 2014;107:119–24. doi:10.1016/j.antiviral.2014.04.008.

8. Sovaldi prescribing information. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf).

9. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M et al. ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889–98. doi:10.1056/NEJMoa1402454.

10. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E et al. ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370(16):1483–93. doi:10.1056/NEJMoa1316366.

11. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS et al. SOLAR-1 Investigators. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology. 2015;149(3):649–59. doi:10.1053/j.gastro.2015.05.010.

12. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E et al. ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370(20):1879–88. doi:10.1056/NEJMoa1402355.

13. Lawitz E, Jacobson IM, Nelson DR, Zeuzem S, Sulkowski MS, Esteban R et al. Development of sofosbuvir for the treatment of hepatitis C virus infection. Ann N Y Acad Sci. 31 July 2015. doi:10.1111/nyas.12832. [Epub ahead of print]

14. Molina JM, Orkin C, Iser DM, Zamora FX, Nelson M, Stephan C et al. PHOTON-2 Study Team. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. Lancet. 2015;385(9973):1098–106. doi:10.1016/S0140-6736(14)62483-1.

15. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ et al. ION-4 Investigators. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373(8):705–13. doi:10.1056/NEJMoa1501315.

16. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R et al. Daclatasvir, sofosbuvir and ribavirin combination for HCV patients with advanced cirrhosis or post-transplant recurrence: ALLY-1 phase 3 study. (Abstract LO8). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

17. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I et al. AI444040 Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370(3):211–21. doi:10.1056/NEJMoa1306218.

18. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH et al. VALENCE Investigators. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370(21):1993–2001. doi:10.1056/NEJMoa1316145.

19. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR et al. ALLY-2 Investigators. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373(8):714–25. doi:10.1056/NEJMoa1503153.

20. Yang HJ, Ryoo JY, Yoo BK. Meta-analysis of the efficacy and safety of sofosbuvir for the treatment of hepatitis C virus infection. Int J Clin Pharm. [Epub 6 June 2015]

21. 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. doi:10.1016/S0140-6736(14)61036-9.

22. Buggisch P, Sarrazin C, Mauss S, Hinrichsen J, Simon K-G, Vermehren J et al. Sofosbuvir-based treatment under real life conditions in Germany (The SOFGER trial). (Abstract PO777). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

23. Dieterich D, Bacon B, Flamm S, Kowdley K, Milligan S, Tsai N et al. Final evaluation of 955 HCV patients treated with 12 week regimens containing sofosbuvir +/- simeprevir in the TRIO network: academic and community treatment of a real-world, heterogeneous population. (Abstract PO775). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

24. Lawitz E, Matusow G, DeJesus E, Yoshida E, Felizarta F, Ghalib R et al. A phase 3, open-label, single-arm study to evaluate the efficacy and safety of 12 weeks of simeprevir (SMV) plus sofobuvir (SOF) in treatment-naive or -experienced patients with chronic HCV genotype 1 infection and cirrhosis: OPTIMIST-2. (Abstract LP04). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

25. Reddy KR. Review article: the efficacy and safety of daclatasvir in the treatment of chronic hepatitis C virus infection. Aliment Pharmacol Ther. 2015;42(3):258–72. doi:10.1111/apt.13264.

26. Saxena V, Koraishy FM, Sise M, Lim JK, Chung RT, Liapakis A et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with reduced renal function: real world experience from HCV-TARGET. (Abstract LP08). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

27. Hedskog C, Dvory-Sobol H, Gontcharova V, Martin R, Ouyang W, Han B et al. Evolution of the HCV viral population from a patient with S282T detected at relapse after sofosbuvir monotherapy. J Viral Hepat. 2015;22(11):871–81. doi:10.1111/jvh.12405.

28. Svarovskaia ES, Dvory-Sobol H, Parkin N, Hebner C, Gontcharova V, Martin R et al. Infrequent development of resistance in genotype 1-6 hepatitis C virus-infected subjects treated with sofosbuvir in phase 2 and 3 clinical trials. Clin Infect Dis. 2014;59(12):1666–74. doi:10.1093/cid/ciu697.

29. Osinusi A, Marti M, Townsend K, Nelson A, Kohli A, Silk R et al. On behalf of the NIAID Hepatitis C SYNERGY Team. Retreatment of relapsers to sofosbuvir/ribavirin with sofosbuvir/ledipasvir: complete and rapid virologic suppression by week 4. (Abstract O11). Report for the EASL 49th International Liver Congress, London, 9–13 April 2014.

30. Wyles D, Pockros P, Morelli G, Younes Z, Svarovskaia E, Yang JC et al. Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. Hepatology. 2015;61(6):1793–97. doi:10.1002/hep.27814.

31. Gane EJ, Hyland RH, An D, Pang PS, Symonds WT, Mchutchison JG et al. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. (Abstract O06). Report for the EASL 49th International Liver Congress, London, 9–13 April 2014.

32. Lawitz E. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks. (Abstract O005). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

33. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N et al. ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61(4):1127–35. doi:10.1002/hep.27726.

34. Ahmad T, Yin P, Saffitz J, Pockros PJ, Lalezari J, Shiffman M et al. Cardiac dysfunction associated with a nucleotide polymerase inhibitor for treatment of hepatitis C. Hepatology. 2015;62(2):409–16. doi:10.1002/hep.27488.

35. Gane EJ, Schwabe C, Stedman C, Weilert F, Stuart K, Cheng W et al. ACH-3422, a novel nucleotide prodrug inhibitor of HCV NS5B polymerase. (Abstract LP27). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

36. Gane EJ, Stedman C, Garg V, George S, Kieffer T, Krop J et al. An interferon- and ribavirin-free 12-week regimen of once-daily VX-135 and daclatasvir in treatment-naive patients with genotype 1 HCV infection. (Abstract P1303). Report for the EASL 49th International Liver Congress, London, 9–13 April 2014.

37. Vertex. Press Release. 1 May 2014 (http://investors.vrtx.com/releasedetail.cfm?ReleaseID = 844664).

38. Changes to the development pipeline FY 2014 update. Status as of 28 January 2015. Roche. (http://www.roche.com/irp150128-annex.pdf),

39. Gane E, Schwabe C, Mader M, Suri V, Donohue M, Huang M et al. Sustained virologic response after ACH-3102 and sofosbuvir treatment for 8 or 6 weeks: a phase 2 “proxy” study. (Abstract PO17). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

40. Gane EJ, Nahass R, Luketic V, Hwang P, Robertson M, Wahl J et al. Efficacy of 12 or 18 weeks of grazoprevir plus elbasvir with ribavirin in treatment-naive, noncirrhotic HCV genotype 3-infected patients. (Abstract PO776). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

41. Poordad F. C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and non-cirrhotic treatment-naïve patients with hepatitis C genotype 1 infection for durations of 4, 6, or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. (Abstract O006). Report for the EASL 50th International Liver Congress, Vienna, 22–25 April 2015.

42. Gane EJ, Hyland RH, An D, Svarovskaia E, McNally J, Brainard DM et al. Once-daily sofosbuvir with GS-5816 with or without ribavirin in patients with HCV genotype 3 without cirrhosis result in high rates of SVR-12: the ELECTRON-2 study. (Abstract 79). Report for the 65th Annual Meeting of AASLD, Boston, 7–11 November 2014.

43. Gane EJ, Hyland RH, Yang Y, Svarovskaia E, Stamm LM, Brainard DM et al. Safety and efficacy of short-duration treatment with GS-9857 combined with sofosbuvir/GS-5816 in treatment-naïve and DAA-experienced patients with and without cirrhosis. (Abstract LPO3). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

44. EASL Recommendations on treatment of hepatitis C 2015. European Society for the Study of the Liver (EASL). (http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf).

45. Aghemo A, De Francesco R. Daclatasvir: a team player rather than a prima donna in the treatment of hepatitis C. Gut. 2015;64(6):860–2. doi:10.1136/gutjnl-2014-307958.

46. Bunchorntavakul C, Reddy KR. Review article: the efficacy and safety of daclatasvir in the treatment of chronic hepatitis C virus infection. Aliment Pharmacol Ther. 2015;42(3):258–72. doi:10.1111/apt.13264.

47. Lawitz E, Sullivan G, Rodriguez-Torres M, Bennett M, Poordad F, Kapoor M et al. Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. J Infect. 2015;70(2):197–205. doi:10.1016/j.jinf.2014.09.008.

48. Gritsenko D, Hughes G. Ledipasvir/Sofosbuvir (harvoni): improving options for hepatitis C virus infection. P T. 2015;40(4):256–76.

49. Leroy V, Dumortier J, Coilly A, Sebagh M, Fougerou-Leurent C, Radenne S et al. Agence Nationale de Recherches sur le SIDA et les Hépatites Virales CO23 Compassionate Use of Protease Inhibitors in Viral C in Liver Transplantation Study Group. Efficacy of sofosbuvir and daclatasvir in patients with fibrosing cholestatic hepatitis C after liver transplantation. Clin Gastroenterol Hepatol. 1 June 2015. pii: S1542-3565(15)00765-X. doi:10.1016/j.cgh.2015.05.030.

50. McCormack PL. Daclatasvir: a review of its use in adult patients with chronic hepatitis C virus infection. Drugs. 2015;75(5):515–24. doi:10.1007/s40265-015-0362-5.

51. Pellicelli AM, Montalbano M, Lionetti R, Durand C, Ferenci P, D'Offizi G et al. Sofosbuvir plus daclatasvir for post-transplant recurrent hepatitis C: potent antiviral activity but no clinical benefit if treatment is given late. Dig Liver Dis. 2014;46(10):923–7. doi:10.1016/j.dld.2014.06.004.

52. Coilly A, Fougerou C, De Ledinghen V, Houssel-Debry P, Duvoux C, Di Martino V et al. The association of sofosbuvir and daclatasvir for treating severe recurrence of HCV infection after liver transplantation. (Abstract G15). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

53. Fontaine H, Lacombe K, Dhiver C, Rosenthal E, Metivier S, Antonini-Michelle T et al. On behalf of Bristol-Myers Squibb and ANRS CO13-HEPAVIH Cohort. Daclatasvir plus sofosbuvir with or without ribavirin in patients with HIV-HCV coinfection: interim analysis of a French multicentre compassionate use program. (Abstract LP23). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

54. Hezode C, De Ledinghen V, Fontaine H, Zoulim F, Lebray P, Boyer N et al. On behalf of BMS and the ANRS CO22-HEPATHER Cohort. Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV genotype 3 infection: interim analysis of a French multicenter compassionate use program. (Abstract LP05). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

55. Welzel T, Herzer K, Ferenci P, Petersen J, Gschwantler M, Cornberg M et al. Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of HCV in patients with severe liver disease: interim results of a multicentre compassion use program. (Abstract P0772). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

56. Fontaine H, Hezode C, Zoulim F, Samuel D, Bouliere M, Haour G et al. On behalf of the ANRS/AFEF HEPATHER Study Group. Efficacy of the oral sofosbuvir-based combination in HCV genotype 4-monoinfected patients from the French observational cohort ANRS CO22 HEPATHER. (Abstract LP28). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

57. Pol S, Bourlière M, Lucier S et al. On behalf of the HEPATHER Study Group. Safety and efficacy of the combination daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients from the French observational cohort ANRS CO22 HEPATHER. (Abstract 103). Report for the EASL 50th International Liver Congress, Vienna, 22–26 April 2015.

58. Summary of product characteristics. Sovaldi. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf).

59. Prescribing information. Daklinza. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206843Orig1s000lbl.pdf).

60. Summary of product characteristics. Daklinza. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003768/WC500172848.pdf).

61. 2013 Pipeline report. HIV i-BASE/Treatment Action Group; June 2013 (http://www.treatmentactiongroup.org/sites/g/files/g450272/f/201306/2013_Pipeline_Report.pdf).

62. Safety and efficacy study of daclatasvir 60 mg, sofosbuvir 400 mg, and ribavirin (dosed based upon weight) in subjects with chronic genotype 3 hepatitis C infection with or without prior treatment experience and compensated advanced cirrhosis for 12 or 16 weeks. ClinicalTrials.gov Identifier: NCT02319031https://clinicaltrials.gov/ct2/show/NCT02319031?term = daclatasvir + AND + cirrhosis&rank = 1.

63. Study to evaluate the safety and efficacy of daclatasvir/sofosbuvir/ribavirin for 16 versus 24 weeks for HCV genotype 3 cirrhotics. ClinicalTrials.gov Identifier: NCT02304159 (https://clinicaltrials.gov/ct2/show/NCT02304159?term = daclatasvir + AND + cirrhosis&rank = 6).

64. Ford N, Swan T, Beyer P, Hirnschall G, Easterbrook P, Wiktor S. Simplification of antiviral hepatitis C virus therapy to support expanded access in resource-limited settings. J Hepatol. 2014;61(Suppl. 1):S132–S138. doi:10.1016/j.jhep.2014.09.019.

65. van de Ven N, Fortunak J, Simmons B, Ford N, Cooke GS, Khee S et al. Minimum target prices for production of direct-acting antivirals and associated diagnostics to combat hepatitis C virus. Hepatology. 2015;61(4):1174–82. doi:10.1002/hep.27641.

66. Merck. Form 10-K, 2014.

67. 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 on 2 February 2015).

68. Wu B. Prescription drug spending jumped in 2014. The Science Times. 14 April 2015 (http://www.sciencetimes.com/articles/5668/20150414/prescription-drug-spending-jumps-2014.htm, accessed on October 2015).

69. Pharmaceutical sector inquiry. Final Report. Brussels: European Commission; 8 July 2009.

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

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

72. Gilead license agreement (full text). Washington DC: Knowledge Ecology International; 2014 (http://keionline.org/sites/default/files/GILD_Sof_License_Agmt_(FINAL).pdf, accessed on 24 October 2015).

73. Chronic hepatitis C treatment expansion. Generic manufacturing for developing countries. Foster City CA: Gilead Sciences Inc.; August 2015 (http://www.gilead.com/~/media/files/pdfs/other/hcv_generic_agreement_fast_facts_72815.pdf, accessed on 4 October 2015).

74. Patent situation of key products for treatment of hepatitis C: sofosbuvir. Working paper, updated version. Prepared by Thomson Reuters. Geneva: World Health Organization; March 2015.

75. Moroccan made hepatitis C medicine in market. Morocco World News. 25 October 2015 (http://www.moroccoworldnews.com/2015/10/171080/moroccan-made-hepatitis-c-medicine-in-market-2/, accessed on 1 November 2015).

76. Natco Pharma launches hepatitis C drug in Nepal. (http://economictimes.indiatimes.com/articleshow/49565267.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst, accessed on 1 November 2015).

77. NATCO launches HEPCINAT LP in Nepal, 28 October 2015 (http://natcopharma.co.in/about/news/, accessed on 31 October 2015).

78. Indian Life Sciences Regulatory Updates & Government Announcements, 2 September 2015 (http://twofourinsight.com/regulatory-updates/welcome-indian-regulatory-updates/july-september-2015/twofour-today-2-september-2015/#SEC1, accessed on 1 November 2015).

79. 14th SEC Gastroenterology & Hepatology. CDSCO (HQ), FDA Bhawan, Kotla road, NewDelhi, 27 August 2015 (http://www.cdsco.nic.in/writereaddata/14th%20SEC%20Agenda%20Gastro%2027_08_2015.pdf, accessed on 1 November 2015).

80. Gokhale K, Chen C. Indian drugmakers engineer hep C cocktails impossible in West. (http://www.bloomberg.com/news/articles/2015-10-09/hep-c-cocktails-impossible-in-west-are-being-engineered-in-india, accessed on 1 November 2015).

81. 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 on 2 February 2015).

82. Hamdy El-Sayed M. Access to hepatitis treatment: the Egyptian experience. Presentation at the joint technical symposium by WHO, WIPO and WTO, Geneva, 28 October 2015.

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

84. Esteban R, Nyberg L, Lalezari J, Ni L, Doehle B, Kanwar B et al. Successful retreatment with sofosbuvir-containing regimens for HCV genotype 2 or 3 infected patients who failed prior sofosbuvir plus ribavirin therapy. (Abstract O8). Report for the EASL 49th International Liver Congress, London, 9–13 April 2014.

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

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

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

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

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

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

91. TREAT Asia/amfAR – The foundation for AIDS Research. Generic sofosbuvir availability and India market pricing as of 10 September 2015 (https://testandtreathepatitisc.files.wordpress.com/2015/03/finindian-generic-sofosbuvir-summary_15sep-10-version.pdf, accessed 4 October 2015).

92. Ghangurde A. Bangladeshi Firms Roll Out $12-13 Harvoni Generic. SCRIP Intelligence. 7 September 2015 (http://www.scripintelligence.com/home/Bangladeshi-Firms-Roll-Out-12-13-Harvoni-Generic-360279, accessed on 10 November 2015).

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

94. Federal Information News & Dispatch. Senate Veterans Affairs Committee Hearing. 4 December 2014.

95. Andrieux-Meyer I, Cohn J, de Araújo ES, Hamid SS. Disparity in market prices for hepatitis C virus direct-acting drugs. Lancet Glob Health. 2015;3(11):e676–e677.

96. Frequently asked questions. Hepatitis Foundation of New Zealand. (http://www.hepatitisfoundation.org.nz/index.php/hepc/faq/, accessed on 4 October 2015).

97. Costly hepatitis C drugs for everyone? Editorial. The New York Times. 2 September 2015 (http://www.nytimes.com/2015/09/02/opinion/costly-hepatitis-c-drugs-for-everyone.html, accessed on 4 October 2015).

98. Quarterly financial results. Q1 and Q2 2015. Foster City CA: Gilead Sciences Inc.

99. Gilead Sciences Inc. Global HCV treatment expansion: a Gilead Sciences update. Presentation at the 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention, Vancouver, 19–22 July 2015.

100. Q2 2015 Earnings results. Slides. Foster City CA: Gilead Sciences Inc.; 28 July 2015 (http://investors.gilead.com/phoenix.zhtml%3Fc%3D69964%26p%3Dirol-earnings, accessed on 1 November 2015).

101. Q3 2015 Earnings results. Slides. Foster City CA: Gilead Sciences Inc.; 27 October 2015 (http://investors.gilead.com/phoenix.zhtml%3Fc%3D69964%26p%3Dirol-earnings, accessed on 1 November 2015).

102. Price of hepatitis C medicine cut by 40pc. Dawn. 5 March 2015 (http://www.dawn.com/news/1167513/price-of-hepatitis-c-medicine-cut-by-40pc, accessed on 4 October 2015).

103. Japan greenlights insurance coverage for new treatment. Nikkei Asian Review. 14 May 2015 (http://asia.nikkei.com/Tech-Science/Science/Japan-greenlights-insurance-coverage-for-new-treatment, accessed on 1 November 2015).

104. Gilead hepatitis C drugs build road to Japan. San Francisco Business Times. 29 July 2015 (http://www.bizjournals.com/sanfrancisco/blog/biotech/2015/07/gilead-gild-japan-sovaldi-harvoni-hepatitis-c.html, accessed on 1 November 2015).

105. Lange C. Is Gilead headed lower from here? 24/7Wallst. 6 July 2015 (http://247wallst.com/healthcare-business/2015/07/06/is-gilead-headed-lower-from-here/, accessed on 1 November 2015).

106. National Assembly Secretariat, Government of Pakistan. Questions for oral answers and their replies. 5 August 2015 (http://www.na.gov.pk/uploads/documents/questions/1438759440_933.pdf, accessed on 4 October 2015).

107. New Hepatitis C drug Sovaldi needed in B.C., say desperate patients. CBC News. 20 February 2015 (http://www.cbc.ca/news/canada/british-columbia/new-hepatitis-c-drug-sovaldi-needed-in-b-c-say-desperate-patients-1.2964065, accessed on 2 November 2015).

108. Health ministry approves new hepatitis C drug under insurance scheme. The Japan Times. 27 August 2015 (http://www.japantimes.co.jp/news/2015/08/27/national/science-health/health-ministry-approves-new-hepatitis-c-drug-insurance-scheme/, accessed on 1 November 2015).

109. HCV Developing World Strategy. Bristol-Myers Squibb. 4 November 2015 (http://www.bms.com/responsibility/access-to-medicines/Pages/HCV-developing-world-strategy.aspx, accessed on 16 November 2015).