New Drugs, New Strategies: Conquering Hepatitis C with Direct-Acting Antivirals

By Tracy Swan

> *Hepatitis C has to be one of the most grossly miscalculated diseases by governments on the planet.*
>
> —Michel Kazatchkine, UN secretary general's special envoy on HIV/AIDS in Eastern Europe and Central Asia and commissioner, Global Commission on Drug Policy

The evolution of hepatitis C virus (HCV) treatment has been swift, dazzling, and unprecedented. In only five years, proof of concept for oral, interferon-free treatment has been established, nine direct-acting antivirals (DAAs) have been approved, treatment duration has been shortened to 12 weeks, and cure rates have been nearly 100% in clinical trials.[1,2,3,4]

Scaling up access to these wonder drugs – and primary prevention – could eliminate HCV, even without a vaccine. Unfortunately, sky-high DAA prices have created a paradox: the more treatment improves, the fewer people have access to it.

A public health approach will be needed to select, procure, and deliver HCV treatment. It is time to pick a first-line regimen, consider options for second-line treatment, and turn up the pressure for universal access to HCV treatment.

HCV Treatment Rationing

> *What is a cynic? A man who knows the price of everything and the value of nothing.*
>
> —Oscar Wilde

Worldwide, 185 million people have been infected with hepatitis C; 73% of them live in middle-income countries (MICs).[5] Pharmaceutical companies see MICs as emerging markets, even though they are home to the "bottom billion" – 73% of the world's poorest people.[6] MIC governments cannot afford DAAs for everyone who needs them.

The price of DAAs in the United States should not be the benchmark anywhere – even in the United States. In high-income countries (HICs), payers have been withholding treatment for hepatitis C, citing sofosbuvir's scandalous launch price (US$1,000 per pill). People who drink alcohol or who use and inject drugs are often ineligible for treatment.

HCV guidelines have been deliberately misinterpreted to justify withholding treatment. DAAs are given only to people with advanced liver disease, to stave off liver cancer, liver failure, transplantation, and death. Limiting HCV treatment access to people with advanced liver damage will stem liver-related mortality, but not epidemics.

HCV Disease Burden and Treatment Access in Egypt

Egypt has the world's highest HCV prevalence: more than 7%.[7,8] In 2006, the country instituted a national hepatitis C program. Since 2008, it has provided treatment for nearly 200,000 people. In 2014, Egypt's government negotiated with Gilead and Janssen to obtain volume-based discounts on their DAAs. Companies can charge higher prices on the private market, where uninsured Egyptians buy their own medicine. In Egypt, 85% of drugs are paid for out of pocket.[9]

Most Egyptians cannot afford HCV treatment. It is a middle-income country where the per capita gross national income (GNI) is US$3,140 – but more than 25% of Egyptians live on less than US$600 a year.[10,11] On the private market, a month of sofosbuvir (Sovaldi) costs EGP2,670 (US$350); simeprevir costs EGP3,166 (US$414).[12,13,14] Government prices are much lower: sofosbuvir costs EGP1,400 (US$184) per month; simeprevir costs EGP1,900 (US$248).[12,13]

The government provides free treatment to people who are unable to afford it, but it cannot do so for millions of people. In 2015, Egypt plans to treat 100,000 people through the national program.[15,16]

Rationing HCV treatment is a stopgap, not a solution – for several reasons:

- If HCV treatment is withheld for too long, it is less effective, and adverse events are worsened.[17,18]
- People with HCV-related cirrhosis remain at risk for liver cancer – *even after being cured* – and must undergo lifelong monitoring. Earlier treatment removes this risk.[19,20]
- HCV lowers quality of life and might cause or worsen many systemic health problems, even in the absence of serious liver disease.[21,22,23,24,25,26,27,28]
- HCV increases health care costs and hospitalization rates, even in people with mild-to-moderate liver disease.[29,30,31,32]
- Chronic HCV infection is associated with a higher incidence of non-liver-related comorbidities (alcohol and substance use disorders, mental illness, chronic kidney disease, obesity, metabolic disorders, pneumonia, and HIV) in people who are 45 to 64 years old.[33]
- People with HCV are dying two decades earlier from non-liver-related causes (including cardiovascular disease and respiratory failure) than people without HCV.[34]
- Many state-funded programs in the United States withhold HCV treatment from people who use alcohol. Withholding treatment based on alcohol use or dependence is harmful because alcohol accelerates HCV liver damage.[34]
    - There is no evidence that alcohol use during DAA treatment impairs efficacy (or safety).
- People who inject drugs are often ineligible for HCV treatment, although they are the highest-prevalence population. Worldwide, HCV prevalence among people who inject drugs is estimated at 67%; anywhere from 6 million to 15 million of them have chronic HCV.[35]
    - Likelihood of HCV reinfection is often a rationale for withholding treatment, although actual reinfection rates are low.[36]

  - People who inject drugs are often ineligible for HCV treatment because of concerns about poor adherence and treatment outcomes. But cure rates in injection drug users are similar to those in nonusers.[37,38]

- Withholding treatment allows HCV to keep spreading, especially among people who inject drugs (since access to injection equipment, methadone, and buprenorphine are woefully inadequate).
- Larger volume and competition between originators and generic drug producers can be leveraged to reduce prices. DAA prices have rapidly dropped by over 40% in some countries.[39,40,41,42] Still, these prices are unsustainable, even for HICs.

Competition, negotiations, and volume-based discounts have begun to bring down originator DAA prices in HICs. Gilead is expected to drop U.S. DAA prices by 46% or more in 2015.[41] Financial analysts estimate that DAA prices will drop to US$45,000 per treatment course in the United States and US$35,000 in HICs elsewhere.[41]

In France and Germany, sofosbuvir alone costs €488 per pill (US$550), or €41,000 (US$46,248) for a 12-week treatment course.[39, 42] In Spain, sofosbuvir costs €297 (US$335) per pill, or €25,000 (US$28,200) for a 12-week treatment course.[40] No information about E.U. prices for simeprevir and daclatasvir (DAAs often used with sofosbuvir) is publicly available.

In 2012, worldwide sales of hepatitis C treatment reached US$4.4 billion and were projected to reach US$10.8 billion by 2022.[43] In just one year, sofosbuvir sales have reached US$10.8 billion.[44] Lack of access to these lifesaving medicines has sparked outrage. Since sofosbuvir was approved, patent challenges, government inquiries, lawsuits, sit-in protests at hospitals, and massive demonstrations have sprung up worldwide.

The right to health *and* clinical evidence should inform access to HCV treatment. Withholding treatment for a curable infectious disease is not justifiable, particularly for one that is often chronic, known to worsen overall health, and potentially life-threatening.

HCV Treatment Strategies: Less Knowledge, More Options

> *We can't make perfectovir the enemy of goodovir.*
>
> —Jennifer Cohn, medical director, Médicines Sans Frontières/Doctors Without Borders Access Campaign

Three decades of antiretroviral drug development for HIV have been augmented by research from publicly funded networks, public-private partnerships, postmarketing trials, registries, and other sources. This robust evidence base informs treatment strategies and guidelines. But HCV DAAs are coming in a very short time frame; there are many choices – but far less knowledge about them. Although real-life data are emerging from registries, compassionate use/early access programs, and postmarketing studies, most of what we know about HCV DAAs comes from registration trials in HICs.

For now, optimizing DAA treatment means selecting the best available regimen and devising a follow-up strategy for new DAAs – or treatment failure (see figure 1).

Goodovir: Sofosbuvir and Daclatasvir

HCV "perfectovir" does not exist – yet.[45] But hepatitis C treatment is already "goodovir" – and it is not likely to improve enough to justify waiting for perfectovir.

Sofosbuvir and daclatasvir together constitute a once-daily, multigenotypic regimen. These DAAs have been effective, safe, and tolerable for thousands of people (including in liver transplant candidates and recipients or HIV/HCV coinfection) (see table 1).[46,47,48]

There is no reason to delay HCV treatment scale-up. A first-line regimen of sofosbuvir and daclatasvir (possibly plus ribavirin [RBV] for people with cirrhosis) will simplify procurement and delivery of HCV treatment. It can be profitably mass-produced for less than US$175.[49]

Table 1. Goodovir and the Future Perfectovir[1,2,3,4,46,47,48,50,51,52,53,54,55,56,57,58,59,60,61,62]

REGIMEN, STATUS, MANUFACTURER	UNIVERSAL		SIMPLE		EFFECTIVE (SVR >90%)	SAFE, TOLERABLE	COMMENTS
	Pangenotypic	Used in HIV	QD	Fixed Duration			
sofosbuvir/daclatasvir (400 mg/60 mg) QD Approved Gilead/BMS	YES (laboratory data only for G5 and G6)	YES	YES	Possibly, with RBV in cirrhosis (especially G3)	YES, except in G3/cirrhosis (without RBV)	YES	RBV may be needed to boost cure rate in cirrhosis (especially for genotype 3)
sofosbuvir/ledipasvir FDC (400 mg/90 mg) QD Approved Gilead	NO (no data in G2)	YES	YES	NO	YES, except in G2 and TX-experienced G3/ cirrhosis	YES	Longer treatment needed in cirrhosis; RBV needed for G3
grazoprevir/elbasvir FDC (100 mg/50 mg) QD Phase III Merck	NO (unless sofosbuvir is added)	YES	YES	NO	NO; less effective in G2; high failure rate in G3; indication sought for G1, G4, and G6	YES	Adding sofosbuvir significantly increased efficacy in G3
sofosbuvir/GS-5816 FDC (400 mg/100 mg) QD Phase III Gilead	YES	NO	YES	?	Depends on duration of treatment, genotype, cirrhosis	YES	Phase II data only
sofosbuvir/GS-5816/FDC + GS-9857 Phase II Gilead	YES	NO	YES	Under study	?	YES	Phase II data only
ABT-530 + ABT-493 Phase II AbbVie	?	NO	?	?	?	?	?
grazoprevir + MK-3682 with elbasvir or MK-8408 Phase II Merck	?	NO	?	?	?	?	?

BMS: Bristol-Myers Squibb
FDC: fixed-dose combination
G: genotype (as in G1, G2, G3, G4, G5, G6)
RBV: ribavirin
SVR: sustained virologic response; undetectable HCV RNA 12 or 24 weeks after finishing treatment, equivalent to cure
TX: treatment
QD: once daily

HCV Drug Resistance

Resistance-associated variants (RAVs) occur naturally in people who have never been treated for hepatitis C. During DAA treatment, RAVs can persist or emerge. In clinical trials, most people with pretreatment RAVs were cured – but RAVs are found in most people who were not cured. The prevalence, longevity, and impact of RAVs differ. Some RAVs have greater impact on drug potency than others.

Baseline resistance testing is not done outside of HCV clinical trials since it is expensive and not always predictive of treatment outcomes.

NS5A resistance

The barrier to resistance varies by class and individual DAA. NS5A inhibitors, although potent, have a low resistance barrier. Many people with pretreatment NS5A RAVs have been cured by an NS5A-containing regimen – but people who are not cured are likely to have NS5A RAVs. In the C-EDGE, ION-1, ION-2, and ION-3 trials of NS5A-containing regimens, most people who were not cured had NS5A RAVS before and after treatment.[1,2,3,53,62] In these trials, treatment failure occurred only in people with an HCV RNA >800,000 IU/mL, suggesting that NS5A RAVs are more likely with a high viral load.

Treatment-emergent NS5A RAVs are persistent for 96–170 weeks after treatment failure.[63,64,65,66] Second-generation NS5A inhibitors might be able to overcome resistance.[67]

NS3 resistance (protease inhibitors)

With HCV protease inhibitors, treatment-emergent RAVs tend to wane within months.[63] People who were not cured by a protease inhibitor–based regimen can be successfully re-treated with DAAs from different classes or with a regimen including a second-generation HCV protease inhibitor with a different resistance profile.[2,68,69]

NS5B resistance (sofosbuvir)

Sofosbuvir has a high resistance barrier and can be recycled in re-treatment regimens. In one trial, 98% (44/45) of sofosbuvir-experienced people were cured by a sofosbuvir-based re-treatment regimen.[70] Although rare, sofosbuvir treatment failure with baseline or emergent RAVs has been documented (especially in genotype 1b).[71,72,73,74]

HCV Treatment in HIV/HCV Coinfection

With DAAs, cure rates do not differ by HIV status, although drug-drug interactions between antiretroviral therapy and HCV treatment need to be avoided or managed.

New HCV Treatment Strategies

Approximately 90% of people are cured by sofosbuvir and daclatasvir (with or without ribavirin); the remaining 10% will need a second-line regimen. There is still a robust HCV pipeline to pluck for second-line DAAs.

Although HCV treatment is moving toward pangenotypic regimens, current strategies are still based on genotype (and sometimes subtype), treatment history, and extent of liver damage. Re-treatment options are limited, especially in genotypes 2 and 3. If pipeline DAAs live up to expectations, it will be possible to select interferon-free first- and second-line regimens.

Figure 1. Current and Proposed Interferon-Free HCV DAA Treatment Strategies

Current first-line strategies for HCV genotype 1

1. **Nucleotide + NS5A inhibitor, with or without RBV**
2. **Protease inhibitor + NS5A inhibitor + non-nucleoside inhibitor, with or without RBV (**complexity, subgenotyping, drug interactions, and RBV use may limit this approach)
3. **Nucleotide + protease inhibitor** (also HCV genotype 4; high DAA prices may limit use of this combination)

Current first-line strategies for HCV non-1 genotypes

1. **Nucleotide + RBV** (suboptimal efficacy in G3/cirrhosis)
2. **Nucleotide + NS5A inhibitor, with or without RBV** (RBV may increase efficacy in G3/cirrhosis)
3. **For G4, protease inhibitor + NS5A inhibitor, with or without RBV**

Next-generation, first-line strategies for all HCV genotypes

1. **Nucleotide + NS5A inhibitor, with or without RBV (NS5A resistance may limit efficacy)**
2. **12 weeks (or less) of a pangenotypic, triple-class regimen (NS5A inhibitor + protease inhibitor + nucleotide polymerase inhibitor). The drawback: this strategy limits options for second-line treatment unless second-generation NS5A and protease inhibitors are effective against RAVs**

Future retreatment strategies for all HCV genotypes

1. **Pangenotypic protease inhibitor (preferably active against RAVs) + nucleotide (for people with NS5A RAVs)**
2. **Pangenotypic protease inhibitor + pangenotypic NS5A inhibitor; both must be effective against NS3 and NS5A RAVs; these could be paired with a nucleotide**

DAAs and Diagnostic Simplification

Costly, complex diagnostic and monitoring requirements are also barriers to HCV treatment, particularly in resource-limited settings. DAAs and innovative diagnostics will make it simpler to identify people with chronic HCV, treat them, and cure them (see figure 2).

- Pre- and posttreatment HCV core-antigen tests could replace anti-HCV and HCV RNA tests.[75]
- Safety monitoring can be less intensive, since adverse event rates are lower and duration of treatment is shorter with DAAs versus interferon.[49]
    - Routine blood tests can be used for pretreatment assessment, identifying people with advanced liver damage (such as APRI or FIB-4), and safety monitoring during treatment.[76]
- Pangenotypic regimens will eliminate the need for pretreatment HCV genotyping and subtyping.

Figure 2. HCV Diagnostics, Assessment for Treatment, and Efficacy Monitoring:* High-Income Country Recommendations versus a Streamlined Process for Resource-Limited Settings[77,78]

High-Income Country Recommendations

HCV antibody testing (to screen)

HCV RNA (to diagnose; with some regimens, may determine duration of treatment and, possibly, whether to add another DAA)

Genotyping/subtyping (to select regimen and duration)

Assess liver damage (to inform duration of treatment)

Assess overall health* (for safety)

HCV RNA testing during and after treatment (to monitor treatment adherence, efficacy, and outcome)

- following E.U. guidelines: at baseline, weeks 2 and 4, EOT, and 12 or 24 weeks after EOT
- following U.S. guidelines: at week 4 and 12 weeks after EOT

Streamlined Process for Resource-Limited Settings

Core antigen (to diagnose HCV)

Assess overall health* and liver damage with routine blood tests (to inform regimen selection and safety monitoring)

Select pangenotypic DAA regimen with fixed duration of treatment (and potential for re-treatment, with longer duration or second-line regimen)

Monitor according to DAA safety profile and patient health

Adherence education, support, counseling

Core-antigen testing 12 or 24 weeks after EOT (to check treatment outcome)

*Additional pretreatment testing is recommended (including pregnancy testing; complete blood count; international normalized ratio; renal function; and levels of albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase).
EOT: end of treatment

HCV Drug Development and Pipeline Strategies

HIV treatment strategies are based on data from industry-sponsored clinical trials, cohort studies, government-funded research networks, public-private partnerships, and investigator-initiated trials. For decades, drugs from different companies have been combined in trials, clinical practice, and fixed-dose combinations (FDCs) from generic and originator companies.

Pharmaceutical companies mastermind DAA development. Clinical collaborations are rare. Incestuous DAA combinations are usually co-formulated to prevent use with a competitor's drug. Other market-driven strategies have delayed or prevented research into and development of optimal DAA combinations.

HCV drug development continues at breakneck speed. DAAs in early development promise to be pangenotypic and active against common RAVs. There is a trend to shorten treatment with multiclass DAA regimens. Several companies are developing – or buying – nucleotide polymerase inhibitors. In the meantime, they are doing "proxy" trials, using sofosbuvir as a placeholder for their own DAAs.

Table 2. Shortening Treatment[58,61,69,79,80,81]

TRIAL, POPULATION, AND MANUFACTURER	PHASE	REGIMEN, POPULATION, AND DURATION			SVR	COMMENTS
"Proxy" Study G1, TX-naive (N = 30) (6 in observation group) Achillion	II	ACH-3102 50 mg + sofosbuvir 400 mg QD		6 weeks	100% (12/12)	Achillion used sofosbuvir as a placeholder for its own nucleotide polymerase inhibitor, ACH-3422 (currently in phase I)
				8 weeks	100% (12/12)	
ELECTRON-2 G3, TX-naive (N = 104) Gilead	II	sofosbuvir 400 mg + GS-5186 25 mg or 100 mg +/– weight-based RBV QD	+ 25 mg	8 weeks	100% (27/27)	This regimen has been studied in other populations. Gilead selected the 100 mg dose of GS-5816 for co-formulation with sofosbuvir; the FDC is currently in phase III
			+ 25 mg & RBV		88% (21/24)	
			+ 100 mg		96% (26/27)	
			+ 100 mg & RBV		100% (26/26)	
G1 and G2 TX-naive noncirrhotic (N = 223) Gilead	II; part B	sofosbuvir 400 mg + GS-5186 25 mg or 100 mg +/– weight-based RBV QD	G1 + 25 mg	8 weeks	77% (20/26)	Longer duration of treatment with this regimen may increase efficacy
			G1 + 25 mg & RBV		88% (22/25)	
			G1 + 100 mg		88% (23/26)	
			G1 + 100 mg & RBV		88% (23/26)	
			G2 + 25 mg		77% (20/26)	
			G2 + 25 mg & RBV		88% (22/25)	
			G2 + 100 mg		88% (23/26)	
			G2 + 100 mg & RBV		88% (23/26)	
G1, TX-naive or DAA-experienced, with or without cirrhosis (N = 75) Gilead	II	sofosbuvir/GS-5186 400 mg/100 mg FDC + GS-9857 100 mg QD	TX-naive	4 weeks	27% (4/15)	Longer treatment and RBV might be needed in cirrhosis, especially in people who are treatment-experienced
			TX-naive	6 weeks	93% (14/15)	
			TX-naive + cirrhosis		87% (13/15)	
			DAA-experienced		68% (17/25)	
			DAA-experienced + cirrhosis		60% (3/5)	
C-SWIFT G1 and G3, TX-naive Noncirrhotic and cirrhotic (N = 143) Merck	II	grazoprevir/elbasvir 100 mg/50 mg FDC + sofosbuvir 400 mg QD	G1	4 weeks	33% (10/30)*	Merck is using sofosbuvir as a placeholder for MK-3682 (currently in phase II) This regimen was less effective for HCV RNA >2,000,000 IU/mL (85% vs. 100%)
			G1	6 weeks	87% (26/30)	
			G1 + cirrhosis	6 weeks	80% (16/20)	
			G1 + cirrhosis	8 weeks	94% (17/18)*	
			G3	8 weeks	93% (14/15)	
			G3	12 weeks	100% (14/14)	
			G3 + cirrhosis	12 weeks	91% (10/12)	
SYNERGY G1, TX-naive (N = 60) NIH	IIa	sofosbuvir/ledipasvir 400 mg/90 mg FDC QD		12 weeks	100% (20/20)	SYNERGY led the way for trials of shorter, multiclass regimens Gilead has not used GS-9669 or GS-9451 in other trials
		sofosbuvir/ledipasvir 400 mg/90 mg FDC + GS-9669 500 mg QD		6 weeks	95% (19/20)	
		sofosbuvir/ledipasvir 400 mg/90 mg FDC + GS-9451 80 mg QD		6 weeks	100% (20/20)	

*modified intent-to-treat analysis; 5 people excluded for nonvirological failure

ACH-3102 (NS5A inhibitor); elbasvir (NS5A inhibitor); grazoprevir (protease inhibitor); GS-5186 (NS5A inhibitor); GS-9451 (protease inhibitor); GS-9669 (non-nucleoside polymerase inhibitor); GS-9857 (protease inhibitor); ledipasvir (NS5A inhibitor); sofosbuvir (nucleotide polymerase inhibitor)

FDC: fixed-dose combination
G: genotype
QD: once daily
SVR: sustained virological response
TX: treatment

Company-Specific Strategies for DAA Development

AbbVie

AbbVie is developing ABT-530 (an NS5A inhibitor) and ABT-493 (a protease inhibitor). In preclinical studies, ABT-530 was active against many NS5A RAVs and pangenotypic; ABT-493 was active against HCV genotypes 1, 2, 3 (especially 3a), 4, and 6 – and common NS3 RAVs.[82,83] These drugs are being studied with or without RBV in phase II trials of all HCV genotypes. An April 8 press release announced a 99% sustained virological response four weeks after treatment (SVR-4) from a phase II trial combining these DAAs.[84]

If AbbVie's pipeline DAAs live up to their pangenotypic, resistance-proof promise, they could be part of second-line treatment. ABT-493 could be paired with sofosbuvir for a pangenotypic re-treatment regimen; if ABT-530 is effective against RAVs, it could be used with sofosbuvir or ABT-493.

Bristol-Myers Squibb (BMS)

Data from thousands of people have supported the safety, tolerability, and efficacy of daclatasvir. Hopefully, it will be available – and affordable – worldwide; it is urgently needed for a pangenotypic first-line regimen.

Daclatasvir's approval – and BMS's overall HCV drug development program – has been stymied by bad luck, inopportune timing, and bold decisions that should have been cautious (and vice versa). The future of the BMS HCV program and its twice-daily, RBV-free TRIO regimen is uncertain. Although SVR in genotype 1b is 98%, TRIO is less effective for genotype 1a than other RBV-free treatment options (SVR: 89% in noncirrhotic; 88% in cirrhotic).[85,86]

Gilead

Gilead's drug development program has been swift, flexible, efficient – and ruthless. The company is seeking to shorten treatment with once-daily, multiclass, pangenotypic FDCs. Gilead's FDC of sofosbuvir and GS-5816 (an NS5A inhibitor) is in phase III. It remains to be seen whether GS-5816 has advantages over daclatasvir (aside from being owned by Gilead). The company is also developing a triple-class combination with the sofosbuvir/GS-5816 FDC and GS-9857 (a protease inhibitor), currently in phase II.

Sofosbuvir has been the backbone of short-course regimens (with grazoprevir/elbasvir; Achillion's NS5A inhibitor, ACH-3102; and Gilead's own drugs, ledipasvir, GS-9669 [a non-nucleoside polymerase inhibitor], or GS-9451 [a protease inhibitor]) (see table 2). Coming up with a short, cure-all regimen has proved to be tricky: six weeks of Gilead's triple-class regimen cured 93% (14/15) of treatment-naive people with HCV genotype 1, but only 68% (17/25) of DAA-experienced people.[69]

Janssen

At the end of 2013, results from the phase II COSMOS trial were used to recommend off-label use of simeprevir with sofosbuvir for genotype 1.[87] Since then, simeprevir has been used in HIV/HCV, cirrhosis, after liver or kidney transplantation, in HCV genotype 4, and with daclatasvir.[88,89,90,91,92,93,94,95]

Janssen will continue to develop DAAs, with a focus on nucleotides. The company has an NS5A inhibitor, JNJ-56914845, in phase II. In November 2014, it purchased Alios BioPharma and acquired two nucleotides: AL-335 (currently in phase I) and AL-516 (currently in preclinical development). In May 2015, Janssen announced a licensing agreement with Achillion, which is developing ACH-3102 (an NA5A inhibitor in phase II) and ACH-3422 (a nucleotide in phase I). Medivir, a past development partner of Janssen's, has a nucleotide (MIV-802) in preclinical development.

Merck

Merck's nautically themed development program for the grazoprevir/elbasvir FDC was bedeviled by dosing problems with grazoprevir and loss of "breakthrough therapy" designation from the U.S. Food and Drug Administration (although Merck subsequently regained it).

It was nearly impossible to figure out the combined impact of host and viral factors, regimen, and duration on SVR in Merck's phase II, multiarm C-WORTHY trial. In phase III trials, a fuller picture of the strengths and vulnerabilities of the FDC emerged. Cure rates in genotype 1b and genotype 4 have been >90%, regardless of HIV status, treatment experience, or cirrhosis.[53,59,62,68] In the oddly named C-SURFER trial, 12 weeks of grazoprevir/elbasvir cured 94% (115/122) of people with HCV genotype 1 and end-stage renal disease, a population with few options and urgent need for HCV treatment.[96] The FDC was less effective against genotype 1a – especially for people with baseline NS5A RAVs known to lower elbasvir potency more than fivefold.[53,62,68] In the C-EDGE treatment-naive trial, overall SVR in HCV genotype 1a was 92% (144/157). It dropped to 58% (11/19) among people with baseline NS5A RAVs and was even lower in people with RAVs associated with lower elbasvir potency (22%; 2/9).[62] In the C-EDGE treatment-experienced trial, SVR dropped from >90% in genotype 1a to 52% (11/21) in people with baseline NS5A RAVs that lower the potency of elbasvir more than fivefold.[53]

On May 28, Merck announced submission of a new drug application for the FDC in genotypes 1, 4, and 6 (the FDC underperformed in genotypes 2, 3, and 5).[51,97,98]

Merck has a strategy beyond launching the FDC: to shorten treatment, with a multiclass regimen. In C-SWIFT, sofosbuvir was added to the FDC for four to 12 weeks of treatment. SVR topped 90% in people with genotype 1 and cirrhosis after only eight weeks of treatment; in people with genotype 3 and cirrhosis, SVR was >90% after 12 weeks of treatment (see table 2).[58]

Merck has DAAs to advance this strategy: MK-8408, a second-generation NS5A that was pangenotypic and active against drug resistance in laboratory studies, and MK-3682, a nucleotide polymerase inhibitor Merck acquired with its 2014 purchase of Idenix.[99] Based on proof of concept from phase I and C-SWIFT, Merck's trials are combining grazoprevir and MK-3682 with elbasvir or MK-8408 for six to eight weeks in ongoing phase II studies in HCV and HIV/HCV, genotypes 1, 2, 3, 4, and 6.[58,100]

Company-Specific Access Strategies for Low- and Middle-Income Countries

World CAB Meeting

In February 2014, the first WORLD CAB meeting was held in Bangkok, Thailand, where activists from low- and middle-income countries (LMICs) met with representatives from AbbVie, BMS, Gilead, Janssen, Merck, and Roche to discuss HCV treatment access. During the meeting, company representatives insisted that access in LMICs would not be possible without a global funding mechanism (such as the U.S. President's Emergency Plan for AIDS Relief or the Global Fund to Fight AIDS, Tuberculosis and Malaria) and that governments needed to "show commitment by scaling up HCV treatment programs before obtaining price reduction."[101]

AbbVie

AbbVie has not disclosed access plans for LMICs. According to a statement on its website from Richard A. Gonzalez, AbbVie's chairman and CEO, the company is "committed to improving lives, and we pledge to go about it in a transparent and sustainable way."[102]

A corporate responsibility brochure describes AbbVie's philanthropic initiatives, including a US$100 million investment in "state-of-the art manufacturing facilities to ensure patients receive a consistent supply of our HIV products"; the "Week of Possibilities" (an adult volunteer program to "transform educational spaces" and "support patients"); and AbbVie Foundation grants for pediatric AIDS, Buruli ulcer detection programs, and disaster relief, but it says nothing about hepatitis C.[103]

BMS

In November 2014, BMS announced its plans for a "Hepatitis C (HCV) Developing World Strategy." The company plans to offer tiered pricing and grant voluntary licenses (VLs) to 90 LMICs – including places where the drug is not patented.[104] Médicines Sans Frontières/Doctors Without Borders (MSF) has described the BMS plan as "a restrictive commercial strategy for sales of its new direct-acting antiviral (DAA) hepatitis C drug daclatasvir in developing countries."[105]

Notably, BMS has not offered VLs to high-burden MICs such as China, Brazil, Egypt, Thailand, and Ukraine. In fact, 50 million people with HCV live in countries where BMS is not offering VLs.[5] Although the country has "initiated discussions with government health authorities and other stakeholders," there is no additional information on plans to license, register, and price daclatasvir.

Gilead

Gilead has not offered VLs to certain high-burden MICs where there are over 50 million people with HCV.[5,106] This means that generic DAAs cannot be sold in these countries. Gilead has blocked other pathways by limiting access to the raw ingredients for its drugs. Gilead's licensees must purchase them from certain suppliers, who are not allowed to sell them to unlicensed generic drug producers. Gilead's extortionate pricing in HICs, unwillingness to provide HCV treatment access to millions of people in MICs, and unethical antidiversion measures (which would not be necessary if its drugs were affordable) are unacceptable.

Janssen

Janssen's website features a global public health section that does not mention hepatitis C.[107] Johnson & Johnson's "Strategic Framework" does not mention HCV. Another part of the company's website ("Pricing Strategies and Programs") describes "strategic, innovative and equitable pricing strategies for a wide variety of diseases" and the access strategy of "a tiered pricing model based on a combination of a country's economic conditions and public health situation."[108,109]

Merck

Merck's website does not provide any HCV-specific access information.

The company's "Statement of Guiding Principles" cites Merck's commitments to research and development, manufacturing and supply, registration, and community investment. Expectations are managed: "While we cannot address complex public health challenges on our own, we will engage in community investment to address the barriers to access where we believe we can make the strongest contributions."[110]

The Medicines Patent Pool and HCV

The Medicines Patent Pool (MPP) is considering expanding its mandate to include negotiating VLs for tuberculosis and hepatitis C. But the MPP has not announced a strategy, goal, or vision for increasing access to DAAs.

MSF has released a statement of support for the MPP's entry into HCV, contingent on consideration of "key issues."[111]

Activists have expressed deep concerns about the MPP entering the "HCV space":

- The MPP's VLs for HIV treatment have excluded most MICs, where access to HCV treatment is needed most. The MPP has not disclosed plans to increase access to HCV treatment in MICs, including countries that have been excluded from the Gilead HCV licensing agreements.
    - Unless the MPP can significantly broaden the geographic scope of the HCV VLs, it will have limited impact on access to HCV treatment.
- The MPP does not directly support other means to increasing access, including patent oppositions and TRIPS flexibilities (allowing countries to produce affordable medicines through a compulsory license, or to import medicines from countries where prices are lower). In fact, some MPP licenses may actually undermine legal TRIPS flexibilities.[112]
    - The MPP's existing HIV licensing agreements with Gilead have the same clauses as Gilead's own HCV licenses; this lowers confidence that the MPP will be able to improve the terms of existing HCV VLs.[110]
    - The MPP's entry into HCV may discourage other community-led approaches, such as pushing governments to issue compulsory licenses. Brazil's compulsory license for efavirenz saved US$100 million, which the country used to provide universal HIV treatment.[113]
- The MPP VLs will attract more generic drug producers. This will limit the remaining sources from which excluded countries can obtain generic DAAs and their raw ingredients.[110]
- The MPP has not made a public statement about the antidiversion measures initially included in Gilead's HCV VLs. These included requiring proof of identity, residence, and citizenship; issuing a one-month

supply of medicine in a smartphone-enabled, coded pill bottle that tracks patients by name, address, and adherence; and refusing to refill medication until empty pill bottles were returned to the local distributor. MSF has issued a briefing document that calls on Gilead to remove these measures.[114]

- VLs are not needed in countries where drugs are not patented. If the MPP offers them, ongoing patent oppositions in LMICs may be undermined.
    - DAAs are covered under patents for years to come: daclatasvir until 2027, sofosbuvir until 2029.[115] Each year, 700,000 people die from HCV-related liver disease.[116] Delaying access to DAAs in LMICs until patent expiry will cost millions of lives.

The same strategies that have led to dramatic price reductions for HIV treatment must be used to provide a cure for millions of people with hepatitis C in LMICs. Generic DAAs can be profitably – and affordably – mass-produced for less than US$200 per treatment course.[49,117]

Conclusion

Curing hepatitis C with safe and effective oral drugs is now possible. The challenge is to secure universal access to HCV treatment and deliver DAAs to the millions of people who need them.

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CROI: Conference on Retroviruses and Opportunistic Infections
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