Hepatitis C Pipeline

By Tracy Swan

BONANZA! The Gold Rush Is Under Way

The direct-acting antiviral (DAA) era officially began in late 2013, with approval of the first all-oral treatment for hepatitis C virus (HCV) genotypes 2 and 3. A hefty pipeline will increase HCV treatment options, especially for people with genotype 1, by mid-to-late 2014. Cure rates above 95 percent—after only 12 weeks of treatment—have become commonplace in HCV clinical trials.* DAAs have been miraculous for people with cirrhosis, HIV/HCV coinfection, and before and after liver transplantation.

But the outrage about sky-high DAA prices is quickly overtaking excitement about these wonder drugs. Advocates and clinicians are forced to fight for access to outrageously expensive drugs for people who cannot wait for affordable options—or watch people die from a curable infection.

Gilead's nucleotide polymerase inhibitor, sofosbuvir—the backbone of most DAA regimens—is US$1,000 per tablet. Such a price limits access to this lifesaving drug, even in high-income countries, where the market for DAAs is projected to reach over US$100 billion by 2023.[1]

Gold Fever!

Analysts at Evaluate Pharma have deemed sofosbuvir "the most valuable research and development product [to date]."[2] At 21 weeks after launch, sofosbuvir sales have reached almost US$3 billion dollars, and analysts predict sales of up to US$9 billion dollars in 2014.[3]

If only 500,000 people in the U.S.—less than a quarter of those with chronic HCV—were treated with sofosbuvir, sales would reach US$45 billion dollars.

*A sustained virologic response (SVR)—meaning that hepatitis C virus becomes undetectable during treatment and remains undetectable for at least 12 weeks after treatment is finished—is equivalent to a cure.

DAAs Offer a Tantalizing Possibility: Global HCV Eradication

At least 185 million people have been infected with hepatitis C virus.[4] HCV is most prevalent in low- and middle-income countries (LMICs).[4] Egypt has the highest hepatitis C prevalence (14%) followed by Cameroon (13.8%), Uganda (6.6%), Uzbekistan (6.5%), the Democratic Republic of Congo (6.4%), and Pakistan (5.9%).[5,6,7] In populous LMICs such as China and India, HCV prevalence is lower, but the sheer number of people with HCV—almost 30 million in China and over 18 million in India—is staggering.[5,6,7]

Less toxic, more effective, and more convenient HCV treatment is a global boon for individual and public health. In April of 2014, the World Health Organization (WHO) issued *Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C*.[8] The *Guidelines* are essential for informing decision makers and health care workers, but high-priced diagnostics and drugs will impede their implementation. "I hope these guidelines will help to promote a reduction in price and thereby an increase in access," said Stefan Wiktor, Team Lead of the WHO Global Hepatitis Programme.[9]

Global eradication of HCV is possible, if pharmaceutical companies will allow generic DAA production in LMICs. "Competition and generic production really are the keys to reductions in prices," says Dr. Wiktor.[10] DAAs can be produced inexpensively, according to an analysis from the University of Liverpool (using molecular weight, chemical structure, complexity, dose, and cost of comparable HIV antiretroviral agents). The actual production cost for 12 weeks of a single DAA ranges from US$10 to US$270, assuming an annual volume of 1–5 million treatment courses (see table 1).[5]

The Médecins Sans Frontières (MSF) Access Campaign has set a target price for the complete package of HCV diagnostics, care, and DAA treatment in LMICs: less than US$500.[11]

Table 1. DAA Regimens: Production Costs and Characteristics[5,12,13,14,15,16,17,18]

Regimen ($/gram)	Cost/Duration	Characteristics
Daclatasvir ($2–6/gram) + **sofosbuvir** ($2-4/gram)	$78–166/12-week	Pangenotypic SVR-24: 89–100% in phase II Ongoing phase III trials in HIV coinfection or cirrhosis/posttransplant May be possible to shorten treatment to 8 weeks in some populations
Daclatasvir + **ribavirin*** ($0.25–0.75/gram) + **sofosbuvir**	$112–224/12-week	Pangenotypic, RBV use may be unnecessary Ongoing phase III trial in cirrhosis/posttransplant

Regimen ($/gram)	Cost/Duration	Characteristics
ribavirin* + sofosbuvir	$102–194/12-week $204–388/24-week	Tx duration varies by HCV genotype; SVR-12, in treatment-naive: Genotype 1 (24 weeks of treatment) : 70% Genotype 2 (12 weeks of treatment): 93% Genotypes 3 and 4 (24 weeks of treatment): >90–100% Less effective in cirrhosis; may be possible to shorten treatment to 8 weeks in some populations
Simeprevir ($10–21/gram) **+ sofosbuvir**	$198–406/12-week	Effective against genotypes 1 and 4 (studied only in genotype 1); SVR-12 in null responders with mild-fibrosis, precirrhosis, and Child–Pugh class A cirrhosis: 93% SVR-12 in treatment-naive, precirrhosis, or Child–Pugh class A cirrhosis: 93%
Ribavirin* + simeprevir + sofosbuvir	$232–600/12-week	Adding RBV did not increase SVR in a phase II trial; ongoing phase III trials do not include RBV

* Weight-based dosing

HCV Diagnostics

Lack of access to HCV viral-load testing has been cited as a barrier to treatment scale-up, since it is essential—viral load is used to diagnose hepatitis C infection and to monitor response to, and outcome of, HCV treatment. Although DAA regimens require less monitoring than PEG-IFN-based treatment, the high price of, and technology required for, HCV viral-load testing curtails the opportunity to diagnose and treat hepatitis C.

AIDS activists—who are fighting to reduce the price of HIV viral-load testing in LMICs—may come to the rescue. Since the same technology can be used for both viruses, affordable HIV viral-load testing offers the potential to increase access to HCV viral-load testing. Other barriers will remain, even with affordable testing: the need for cold-chain transportation, expensive machinery, laboratory space, trained personnel, and stable electricity.

Lack of innovation in diagnostics is hindering global efforts to screen, diagnose, and treat HCV. Development of reliable, less complicated rapid and point-of-care testing is long overdue. The WHO has developed criteria for evaluating HIV point-of-care devices, known as ASSURED (affordable, sensitive, specific, user-friendly, rapid, and robust, equipment-free, and deliverable to end users).[19]

Choosing the Best First-Line DAA Regimen

I have the simplest tastes. I am always satisfied with the best.
—Oscar Wilde

Global progress against HCV has been hobbled by complex diagnostics and monitoring requirements, and suboptimal, expensive, and difficult-to-tolerate treatment. DAAs can radically simplify HCV treatment and reduce diagnostic and monitoring requirements. In the United States, the demand for HCV treatment is likely to outstrip the capacity of specialists to deliver it. Simple DAA regimens will make it easier for nonspecialist providers to begin treating HCV in people with less advanced liver disease.

The characteristics of optimal HCV regimens for resource-limited settings—simplicity, convenience, and manageability—are also relevant for high-income countries. Desirable characteristics for DAA regimens (assuming affordability, safety, and tolerability) include:

- Highly effective—cure rate of >80%—regardless of host and viral factors, especially in populations most likely to be prioritized for treatment (e.g., people with cirrhosis or HIV/HCV);
- Pangenotypic, potent regimens with a high barrier to drug resistance;
- Simple regimens that obviate a battery of pretreatment testing (IL-28B genotyping, viral subtyping, and drug resistance), and do not require extensive monitoring for safety, efficacy, and treatment outcome;
- Manageable drug-drug interactions, allowing coadministration with commonly used medications (treatment for HIV and tuberculosis, methadone, buprenorphine, statins, hormonal contraception, and psychotropic medications);
- Safety during pregnancy and nursing;
- Safety and efficacy in pediatrics;
- Fixed treatment duration (preferably ≤12 weeks);
- No food requirement;
- No cold storage needed;
- Once-daily dosing; and
- Low pill burden.

Table 2. DAA Regimens: Desirable Characteristics

Regimen/ Sponsor(s)	Status	Pangenotypic	Safe, effective in advanced liver disease	Acceptable tolerability (data may be limited)	Manageable drug-drug interactions	Duration ≤12 weeks	QD	Studied in HIV/HCV	SVR ≥90%
Fixed-dose combination (FDC): ABT-267/ABT-333/ ABT-450/r + RBV AbbVie	2014 Expected approval		X	X	?	X		X	X
Asunaprevir + BMS-791325 + daclatasvir BMS	2015 Expected approval		?	X	?	X			X
Daclatasvir + sofosbuvir BMS	2014 Expected approval	G1-3; ongoing trials in all genotypes	X	X	X	X	X	X	X
FDC: sofosbuvir/ ledipasvir Gilead	2014 Expected approval		X	X	?	X	X	X	X
FDC: sofosbuvir/ GS-5816 Gilead	2015 Possible approval	X	?	X	?	X	X	X	X
Sofosbuvir + RBV Gilead	Approved 2013	X	X	X	X			X	Only in G2
Sofosbuvir + PEG/IFN/RBV Gilead/Roche/ Merck; generics	Approved 2013	X	?	?	X	X		X	X
Sofosbuvir + simeprevir (off-label) Gilead/Janssen	Approved 2013		X*	X	X	X	X	X	X
MK-5172 + MK-8742 Merck	2015 Expected approval	Studies in G4–6 planned; also being studied with sofosbuvir in G3	?	X	?	?	X	X	X

*Child–Pugh class A cirrhosis only

There are no data on these regimens in people who inject drugs, during pregnancy and nursing, or in pediatrics (ribavirin is contraindicated in pregnancy, during nursing and in children under three years old). There are virtually no data on DAA safety, efficacy, and tolerability in people with common comorbidities.

Sofosbuvir, simeprevir, and ribavirin can be stored at room temperature (below 84°F or 28°C); sofosbuvir can be taken with or without food; ribavirin and simeprevir should be taken with food. Data on food and storage requirements for experimental DAAs are not available. All regimens have a low pill burden and require limited monitoring during treatment.

From the Graveyard to the Gravy Train: Nucleoside/tide Polymerase Inhibitors

Sofosbuvir—the only approved nucleoside/tide polymerase inhibitor—is pangenotypic, potent, has a high resistance barrier, few drug-drug interactions, and has proven to be safe and tolerable.

Developing HCV nucleoside/tide polymerase inhibitors is tricky, despite their potential. DAAs from this class (particularly guanosine-based nucleotides) have been discontinued because they were too toxic (BMS-986094 [renal and cardiac toxicity]; NM283 [gastrointestinal toxicity]; R1626 [lymphopenia and neutropenia]; PSI-983 [liver toxicity]).[20,21] Mericitabine is the only other nucleotide to have advanced into phase III, but further development seems to be stalled, possibly permanently. VX-135, a once promising candidate, has entered pharmaceutical limbo since Vertex announced plans to license it out.

But there may be more nucleotides: after setbacks with NM283, IDX184, and IDX19368—all discontinued—Idenix forged ahead with development of two uridine nucleotide polymerase inhibitors (IDX21437 and IDX21459). In June of 2014, Merck purchased Idenix. Achillion has a uridine nucleotide, ACH-3422, in a phase I trial.

HCV TREATMENT LANDSCAPE

Note: Comprehensive information on DAA regimens is available online, at http://www.pipelinereport.org/2014/hcv/update.

Genotype 1: There Is No Balm in Gilead

Despite the remarkably rapid progress against HCV, patients with genotype 1 and cirrhosis—who urgently need treatment to avert transplantation, liver cancer, and death—are still waiting for DAAs, since peginterferon may be too dangerous, too toxic, or ineffective. Yet there is an effective DAA regimen for genotype 1—even in null responders with compensated cirrhosis.

In COSMOS, a phase II trial, Janssen's simeprevir and Gilead's sofosbuvir were highly effective and safe for people with HCV genotype 1 and compensated cirrhosis, regardless of treatment history; cure rates over 90 percent were reported after 12 weeks of treatment.[22,23] Despite the need for, and promise, of this regimen, Gilead declined to continue codevelopment with Janssen.

Simeprevir and sofosbuvir have been approved separately. The combination was not approved by regulatory agencies, but treatment guidelines in the United States and the European Union recommend off-label use for people with HCV genotype 1 who are ineligible for interferon-based treatment.[24,25] Gilead's monopolistic approach has limited awareness of off-label HCV treatment options among physicians; according to a Decision Resources report, "a notable share" of gastroenterologists and infectious disease specialists continue to prescribe suboptimal boceprevir- and telaprevir-based treatment to genotype 1 patients (these regimens are no longer recommended by the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, or the European Association for the Study of the Liver).[26]

Collaboration between sponsors facilitates development of potentially lifesaving regimens. Unfortunately, commercial interests have trumped medical need—it is unacceptable that Gilead's desire to dominate the HCV market has delayed or complicated access to the best possible treatment.

Climb Every Mountain: Curing Genotype 3

Despite a gushing pipeline, there are still critical gaps in HCV treatment—especially in genotype 3, which has global distribution. An interferon-free cure-all for genotype 3—especially for people with cirrhosis—remains elusive, although there are DAA regimens in clinical trials. BMS is sponsoring ALLY-3, a 150-person phase III trial of daclatasvir and sofosbuvir in genotype 3 (treatment-naive and treatment-experienced). Merck is launching a phase IIb trial of sofosbuvir with a fixed-dose combination of MK-5172 (protease inhibitor) and MK-8742 (NS5A inhibitor) for 8 or 12 weeks.

There are three strategies for increasing efficacy of sofosbuvir-based treatment in genotype 3: adding peginterferon to a 12-week regimen of sofosbuvir and ribavirin; combining sofosbuvir with another DAA (daclatasvir, ledipasvir, or GS-5816); or extending the duration of treatment with sofosbuvir and ribavirin to 16 or 24 weeks. Each strategy has limitations. Peginterferon is unappealing to, or contraindicated for, many people; daclatasvir, ledipasvir, and GS-5816 are not yet approved (limiting access to people who are eligible for clinical trials, or early access and named-patient programs), and the cost of a 24-week regimen (US$168,000 for sofosbuvir) is likely to make payers balk.

High drug prices—not the basic human right to health care—are the bedrock of cost per cure.* Other factors, such as a country's disease burden, and the resources it has for hepatitis C are not considered. Cost per cure attempts to transform unaffordable medicines into bargains, by reducing health care costs in the future (for example, HCV cost per cure is less expensive than liver transplantation).

* "Cost per cure" is calculated by dividing a standard cost reference by the sustained virologic response (or cure) rate in a specific population, then multiplying it by 100.

Table 3. Genotype 3: Regimen, SVR-12, Relapse, and Cost[15,16,18,27,28,29,30,31,32]

Regimen/Duration	Population	SVR-12	Relapse	Estimated cost (U.S.-only; RBV 1,000 mg/day)*	Cost per cure (drugs only)
PEG-IFN/RBV, 24 weeks	Tx-naive	63% (110/176)	9% (16/176)	$20,478	$32,504
SOF + PEG-IFN/RBV, 12 weeks	Tx-naive	100% (18/18)	0%	$94,239	$94,239
	Tx-experienced	83% (20/24)	8% (2/24)		$113,540
SOF + RBV, 12 weeks	Tx-naive	56% (102/183)	40% (72/179)	$84,449	$150,801
	Tx- naive, HIV-positive	67% (28/42)	26% (11/42)		$126,043
	Tx-experienced	30% (19/64)	68% (44/64)		$281,496
SOF + RBV, 16 weeks	Tx-experienced	62% (39/63)	38% (24/63)	$112,598	$181,610
SOF + RBV, 24 weeks	Tx-naive	93% (98/105)	5% (5/105)	$168, 898	$181,610
	Tx-experienced	77% (112/145)	20% (29/144)		$219,348
SOF + DCV 3 RBV, 24 weeks	Tx-naive	89% (16/18)	<1% (1/18)	$211,974/$212,872**	$238,173/$239,182
SOF/LDV 3 RBV, 12 weeks	Tx-naive	64% (16/25)	32% (8/24)	?	?
	Tx-naive (+ RBV)	100% (26/26)			
SOF + GS-5816 (25 mg or 100 mg), 12 weeks	Tx-naive, 25 mg dose	93% (25/27)	<1% (1/27)	?	?
	Tx-naive, 100 mg dose	93% (25/27)	<1% (1/27)		

*Data from www.goodrx.com (Accessed on May 2, 2014).

**Daclatasvir price is based on the cost to France's ATU program, which is €35,000 (US$47,974.52) per patient, regardless of dose (Source: www.seronet.info/article/traiter-lhepatite-c-sans-interferon-des-atu-pour-le-simeprevir-et-le-daclatasvir-66334; accessed on May 3, 2014).

HIV: Not Special, Anymore

People with HIV and hepatitis C (especially genotype 1) are less likely to be cured by peginterferon and ribavirin treatment. In the DAA era, HIV is no longer a poor prognostic factor for response to HCV treatment. Adding a protease inhibitor to PEG-IFN and RBV has produced similar SVR rates, regardless of HIV status.[33,34,35,36]

Now, proof of concept has been established for efficacy of peginterferon-free regimens in people with HIV and HCV (see table 4). In fact, cure rates from some of the clinical trials in HIV/HCV have been higher than those in HCV monoinfection, probably due to experience with, and support for, adherence to antiretroviral therapy.

Table 4. SVR from Interferon-Free Trials in HIV/HCV[15,37,38]

Trial (N, regimen, population, phase, sponsor)	Treatment arm	SVR	Comments	ARVs allowed
PHOTON-1 Sofosbuvir + RBV N = 182 HCV genotype 1 ,2, & 3, Tx-naive, cirrhosis: 6% (12/182) Phase II Gilead	24 weeks, 2 drugs (G1)	SVR-12: 76% (87/114)	Less effective in IL28B non-CC genotypes, Black (vs. non-Black) participants, people with cirrhosis, males, and G1b	atazanavir/r, efavirenz, emtricitabine, darunavir/r, raltegravir, rilpivirine, tenofovir
	12 weeks, 2 drugs (G2)	SVR-12: 88% (23/26)		
	12 weeks, 2 drugs (G3)	SVR-12: 67% (28/42)		
C-WORTHY MK-5172 + MK-8742 ± RBV N = 59 HCV genotype 1, Tx-naive, noncirrhotic Phase II Merck	12 weeks, 2 drugs	SVR-12: 90% (26/29)	1 relapse in RBV arm; 2 virologic breakthrough in no-RBV arm; all were in G1a	abacavir, emtricitabine, raltegravir, tenofovir
	12 weeks, 3 drugs	SVR-12: 97% (28/29)		
ERADICATE FDC: Sofosbuvir/ ledipasvir N = 50 HCV genotype 1, Tx-naive, noncirrhotic Phase II Interim Data	12 weeks, 2 drugs ARV-treated, on current regimen for ≥8 weeks, CD4 >100/mm^3; HIV RNA <40 copies/mL	SVR-4: 100% (22/22)		efavirenz, emtricitabine, raltegravir, rilpivirine, tenofovir
	12 weeks, 2 drugs no ARVs, stable CD4 with HIV RNA <500 copies/mL or CD4 >500/mm^3	SVR-4: 100% (10/10)		

The only consideration for treating people coinfected with HIV and HCV is avoiding—or managing—drug-drug interactions between DAAs and antiretrovirals (ARVs). To date, the only pangenotypic DAA-based regimen that can be used without restrictions with ARVs (except AZT and ddI which are contraindicated with ribavirin) is 12 weeks of sofosbuvir, peginterferon, and ribavirin.

As of mid-2014, several trials are open or planned in people with HIV/HCV.

Table 5. Ongoing and Planned Trials in HIV/HCV Coinfection

Regimen, sponsor, phase	Population
TURQUOISE-I ABT-450/r/ABT-267 + ABT-333 + RBV AbbVie Phase III	Genotype 1, treatment-naive and treatment-experienced (+ PEG-IFN/RBV)
SWIFT-C Sofosbuvir + RBV AIDS Clinical Trials Group Phase I	Acute HCV infection (or reinfection); genotype not specified
Asunaprevir + daclatasvir BMS Phase II	Genotype 1b, treatment-naive and treatment-experienced (+ PEG-IFN/RBV); no ARV or raltegravir + tenofovir/emtricitabine or abacavir/lamivudine
ALLY-2 Daclatasvir + sofosbuvir BMS Phase III	Genotypes 1–6: treatment-naive and treatment-experienced
FDC: Sofosbuvir/ledipasvir Gilead Phase II	Genotype 1, treatment-naive
FDC: Sofosbuvir/ledipasvir or sofosbuvir + RBV Gilead Phase II	Genotypes 1, 4 (FDC) and genotypes 2, 3 (sofosbuvir + RBV); treatment-naive or treatment experienced (+ PEG-IFN/RBV); inherited bleeding disorder
FDC: Sofosbuvir/ledipasvir Gilead Phase II	Genotype 1, treatment-experienced (PEG-IFN/RBV + HCV protease inhibitor)
Sofosbuvir + RBV Gilead Phase III	Genotype 1-4 treatment-naive Genotype 2 and 3, treatment-experienced
FDC: Sofosbuvir/ledipasvir Gilead Phase III	Genotype 1 and 4, treatment-naive and treatment-experienced (+ RBV)
C-EDGE COINFECTION MK-5123 + MK-8742 Merck Phase III	Genotype 1, 4, 5, and 6; treatment-naive

Source: www.clinicaltrials.gov.

Hepatitis C Trials: Not Just for Middle-Aged, Non-Cirrhotic White Males?

A majority of the participants in HCV clinical trials are middle-aged white males. Enrollment of people from other racial and ethnic groups is shamefully inadequate. There are no data on participation in, or outcomes from, HCV clinical trials among Native Americans and Alaska Natives, although they share the highest incidence of, and mortality from, HCV in the United States.[39]

African Americans

Information about how DAAs perform in the people most likely to use them is critical, yet it often is unavailable until postmarketing studies have been completed. African Americans are underrepresented in clinical trials, despite high HCV prevalence (22% of cases in the U.S.).[40] Enrollment of African Americans hovers below 20 percent in all but one industry-sponsored trial, Gilead's PHOTON.

Hepatitis C infection is more likely to become chronic, and peginterferon-based treatment is less effective for people with the IL28B TT genotype and other genetic polymorphisms found more frequently among African Americans than people of other races and ethnicities.[41] African Americans with HCV have poor posttransplant survival rates, and significantly higher incidence of, and mortality from liver cancer than their white counterparts.[42,43]

Hispanics

Hispanics are twice as likely to die from viral hepatitis than non-Hispanic Whites.[44] HCV progresses more rapidly in Hispanics than African Americans or Whites, and they are more likely to develop cirrhosis.[45] Type 2 diabetes (which is associated with poor response to peginterferon) is prevalent among Hispanics, underscoring the need for more effective HCV treatment, yet they are often underrepresented in clinical trials.

Women

Although HCV trials enroll a substantial proportion of women, sponsors fail to break out race and ethnicity data by gender, obscuring possible differences in efficacy. Sex- and age-specific side effects are not well characterized in HCV clinical trials, leaving women without adequate information to inform their HCV treatment decisions.

Table 6. Participation in HCV Clinical Trials by Gender, Race, and Ethnicity; Genotype 1[13,15,16,33,34,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64]

Trial: N, Population, and Phase	Women	African American/ Black	Hispanic/ Latino/Latina	Asian	Other
Sponsor: ABBVIE					
PEARL-II (N = 186) G1b only; Tx-experienced, noncirrhotic Phase III	45% (84/186)	91% (170/186) white; no other race/ethnicity reported			
PEARL-III (N = 419) G1b only; Tx-naive, noncirrhotic Phase III	56.5% (237/419)	5% (20/419)	1.5% (7/419)	6.5% (28/419)	
PEARL-IV (N = 305) G1a only; Tx-naive, noncirrhotic Phase III	35%(106/305)	12% (36/305)	9% (28/305)		4% (12/305)
SAPPHIRE-I (N = 631) Tx-naive, noncirrhotic Phase III	45.5% (287/631)	5.5% (34/631)	5% (32/631)		
SAPPHIRE-II (N = 394) Tx-experienced, noncirrhotic Phase III	42% (167/394)	8% (32/394)	6% (25/394)	1.5% (6/394)	
TURQUOISE-II (N = 380) Tx-naive and Tx-experienced; compensated cirrhosis Phase III	30% (113/380)	3% (12/380)	12% (45/380)	2% (8/380)	
Sponsor: BMS					
AI444040 (N = 167) G1a only; Tx-naive and Tx-experienced, noncirrhotic Phase II	47% (78/167)	14% (24/167)			4% (6/167)
A1443-014 (N = 166) Tx-naive; 9%; cirrhosis Phase II	33% (54/166)	16% (27/166)		1% (2/166)	
HALLMARK DUAL (N = 745) G1b only; Tx-naive and Tx-experienced; 30% cirrhosis Phase III	55% (411/745)	6% (42/745)		25% (186/745)	

Trial: N, Population, and Phase	Women	African American/ Black	Hispanic/ Latino/Latina	Asian	Other
Sponsor: BOEHRINGER INGELHEIM					
STARTVerso 1 and 2 (N = 1,309) Tx-naive; 9% cirrhosis Phase III	44% (578/1309)	7% (94/1309)			
STARTVerso 3 (N = 678) Tx-experienced; 21% cirrhosis Phase III	42% (275/678)	<4% (24/678)		18% (124/678)	
STARTVerso 4 (N = 308) HIV-positive, Tx-naive or relapse; 17% cirrhosis Phase III	19% (60/308)	14% (42/308)		2% (7/308)	1% (3/308)
Sponsor: GILEAD					
NEUTRINO (N = 327) G1 (N = 292); Tx-naive; 17% cirrhosis Phase III	36% (118/327)	17% (54/327)	14% (46/327)	2% (7/327)	3% (9/327)
ION-1 (N = 865) Tx-naive; 16% cirrhosis Phase III	40.5% (352/865)	12.5% (108/865)	12% (101/865)	<2% (11/865)	<2% (11/865)
ION-2 (N = 440) Tx- experienced; 20% cirrhosis Phase III	35% (153/440)	17% (77/440)	9% (41/440)	<0.5% (1/440)	<1% (2 other, one Hawaiian/ Asian Pacific Islander)
ION-3 (N = 647) Tx-naive; noncirrhotic Phase III	42% (272/647)	19% (123/647)	6% (39/647)		2.5% (17/647)
PHOTON-1 (N = 114) HIV-positive, Tx-naive; 4% cirrhosis Phase III	18% (21/114)	33% (37/114)	22% (25/114)		
Sponsor: JANSSEN					
C0212 (N = 106) HIV-positive; Tx naive and tx-experienced; 10% cirrhosis Phase II	15% (16/106)	14% (14/106)			
COSMOS (N = 167) Tx-naive and Tx-experienced; 40% cirrhosis Phase II	36% (60/167)	19% (31/167)	21% (35/167)		

Trial: N, Population, and Phase	Women	African American/ Black	Hispanic/ Latino/Latina	Asian	Other
PROMISE (N = 393) Relapsers; 15% cirrhosis Phase III	34% (133/393)	3% (13/393)	6% (24/393)	3% (11/393)	1% (1 Asian Pacific Islander; 1 mixed-race)
QUEST-1 (N = 394) Tx-naive; 12% cirrhosis Phase III	43.5%(172/394)	8% (30/393)		2% (7/393)	
QUEST-2 (N = 391) Tx-naive; 8% cirrhosis Phase III	44% (171/391)	91.5% (329/ 360) white; no other race/ethnicity reported			
Sponsor: MERCK					
C-WORTHY (N = 159) Tx-naive; noncirrhotic Phase II	50% (78/159)	7% (11/159)	10% (15/159)	<3% (4/159)	
C-WORTHY (N = 253) Tx-naive and null responders; 40% cirrhosis Phase II	41% (105/253)	6% (15/253)	5% (12/253)		2% (5/253)
Sponsor: NIAID					
SPARE (N = 60) Tx-naive; 22% precirrhosis or cirrhosis Phase II	38% (23/60)	83% (50/60)	4% (2/60)		
SYNERGY (N = 60) Tx-naive; 5% cirrhosis Phase II	29% (17/60)	89% (53/60)			

ADVERSE EVENTS

The expression "generally well tolerated" is used to describe virtually any adverse event (AE) that doesn't kill participants in HCV clinical trials. AE reports from DAA trials tend to be overshadowed by the astonishing cure rates and ever-shorter treatment durations. Years of looking at long, long lists of AEs and high discontinuation rates from trials of peginterferon and ribavirin-based regimens have numbed conference attendees (who are also not the ones experiencing them). But these adverse events are likely to be worse in the real

world, given that people in clinical trials are usually healthier, monitored more closely, and cared for by more experienced clinicians.

In phase II and phase III trials of DAAs, at least five percent of study participants experienced an adverse event (see table 7). Adverse events are not always reported in terms of severity and duration, and it is unclear how many people are bedeviled by multiple AEs.

Ribavirin the Terrible

Although peginterferon is quickly becoming a therapeutic relic, ribavirin is still in the mix. It may be more toxic than anyone realized. Some of the AEs associated with peginterferon (irritability, anxiety, depression, insomnia, nausea, muscle and joint pain) have now been reported in ribavirin-containing arms of peginterferon-free trials.

Even without ribavirin, it is difficult to identify which drug or drugs are the culprits, since DAAs are not used alone.

Table 7. Adverse Events in ≥5 Percent of Participants, from a Sampling of Phase II and Phase III DAA Trials (Alphabetical Order)[15,18,27,28,30,49,50,57,63,65,66,67]

	Treatment-Naive	Treatment-Experienced
RBV-free	Abdominal distention, abdominal pain, anxiety, asthenia, back pain, common cold, constipation, cough, diarrhea, dizziness, dysmenorrhea, dyspepsia, nasopharyngitis, night sweats, fatigue, headache, insomnia, irritability, nausea, oropharyngeal pain, pain, pruritus, rash, shoulder pain, upper abdominal pain, vomiting	Abdominal distention, anxiety, arthralgia, back pain, constipation, cough, diarrhea, dizziness, dry skin, dysmenorrhea, dyspepsia, fatigue, headache, insomnia, irritability, nasopharyngitis, nausea, oropharyngeal pain, pain, pruritus, rash, upper abdominal pain, vomiting
RBV-containing	Anemia, arthralgia, asthenia, back pain, decreased appetite, diarrhea, dizziness, dyspepsia, fatigue, headache, insomnia, irritability, myalgia, nausea, pruritus, pyrexia, rash, upper respiratory tract infection	Anemia, arthralgia, asthenia, cough, depression, diarrhea, dizziness, fatigue, headache, insomnia, irritability, nausea, pain, pruritus, rash, upper respiratory tract infection

People Who Inject Drugs

In the developed world, 80 percent of new HCV infections occur in people who inject drugs (PWID), due to lack of access to sterile injection equipment.[68] Worldwide, 10 to 15 million PWID have been infected with hepatitis C virus.[69] Yet only two to four percent of PWID have been treated, due to a range of structural, socioeconomic, cultural, legal, and other barriers.[70] Concerns about poor adherence lead some physicians to withhold treatment from PWID, regardless of evidence that adherence and HCV treatment outcomes among people who inject drugs are similar to those among people who are not injecting drugs.[71]

From TasP to CasP

I don't want to be called a transmitter—that's electricity.
—Jude Byrne, Senior Project Officer, National Hepatitis C and Other BBVs/STIs Program, Australian Injecting & Illicit Drug Users League (AIVL)

Research on HIV treatment as prevention (TasP) has inspired modelers to look at the impact of HCV treatment on prevalence among people who inject drugs. Unlike HIV, hepatitis C can be cured; only a few months of oral drugs are needed to accomplish this. Mathematical models indicate that treating a small proportion of PWID will significantly reduce HCV prevalence, given the high SVR rates seen in DAA clinical trials.[72]

HCV cure as prevention (CasP) is an advocacy platform for ramping up access to both HCV prevention and treatment for PWID. But barriers such as criminalization and discrimination will stymie efforts to implement CasP among PWID. It is critical that people who inject drugs be involved in the design, implementation, and oversight of CasP programs, and that these programs be linked to larger social justice movements.

Pregnancy and Pediatrics

Each year, 60,000 infants are born with HCV infection. In HCV-monoinfected women, the rate of vertical transmission is three to five percent; HIV coinfection doubles the risk.[73,74] It may be possible to prevent vertical transmission with ribavirin-free DAA regimens, but there have not been any trials so far.

The standard of care for children from 3 to 17 years of age is peginterferon and ribavirin, which has many side effects and may inhibit growth.[75] Earlier HCV regimens were not ideal for use in pediatrics (or adults). Newer DAA regimens should be studied in pediatrics.

CONCLUSION

Although the HIV experience is valuable for tackling HCV, there are significant differences between these viruses and responses to them. HIV activists have mobilized worldwide using a human rights–based framework, wielding evidence from global research networks to fight for programs that prevent, diagnose, and treat HIV. In contrast, the dialogue about HCV has been primarily focused on cost-effectiveness, due to high prices and flaccid responses from governments and donors.

The hard work—transforming the HCV treatment cascade from scarcely a dribble into a waterfall—is just beginning. Access to affordable HCV viral-load testing and treatment can become a reality, so long as people are willing to fight for them.

The lessons learned from AIDS treatment activism and scale-up are relevant to hepatitis C: drugs cannot stop an epidemic by themselves, no matter how good they are. Activists, donors, governments, implementers, and clinicians must work together to make sure that HCV treatment reaches all who need it.

RECOMMENDATIONS

Research

1. Support public-private research partnerships for HCV diagnostics and treatment; leaving drug development solely to the pharmaceutical industry does not serve public health, and may be hazardous.
2. Focus on development of HCV diagnostics for resource-limited settings, using the WHO ASSURED criteria; pilot HCV treatment projects are opportunities to simultaneously validate innovative HCV diagnostics.
3. Identify and study the best DAAs for preventing vertical transmission.
4. Launch pediatric trials in HCV and HIV/HCV coinfection (with the most suitable candidates).
5. Study DAA regimens in people with HCV genotypes 5 and 6.
6. Develop DAAs in different formulations (long-acting, single-injection) to facilitate HCV treatment scale-up.
7. Enroll representative populations in HCV clinical trials, especially people with advanced liver disease from high-prevalence populations.

Policy and Implementation

1. Governments must not continue to ignore HCV; it is time for national plans to address the epidemic. People with HCV and their allies, people who inject drugs, epidemiologists, medical providers, researchers, and policy makers need to participate in development and implementation of their national plans.
2. Donors need to support and coordinate efforts to increase global access to HCV prevention, diagnostics, care, and treatment in LMICs.
3. Pharmaceutical companies must allow generic competition, since they have ample opportunity to recoup investment in, and amply profit from their DAAs.
4. Implementers must gear up; it is time to initiate widespread capacity building so that nonspecialist providers, community health care workers, and peers can deliver HCV education, screening, care, and treatment.
5. People who inject drugs must have the opportunity to participate in the design, implementation, and oversight of HCV prevention, testing, and treatment programs intended for them.

ENDNOTES

1. Bloomberg Personal Finance. Saving and Investing. J & J, Medivir win U.S. FDA approval for hepatitis C pill. Available at: http://www.bloomberg.com/news/2013-11-22/j-j-medivir-win-u-s-approval-for-hepatitis-c-pill.html. (Accessed on 2013 December 1)
2. Evaluate Pharma. World preview 2013 Outlook to 2018 – returning to growth. Available at: http://www.evaluategroup.com/public/reports/Evaluate-World-Preview-2013-Outlook-to-2018.aspx. (Accessed on 2014 January 10)
3. Barron's. Stocks to watch: Gilead Sciences' Sovaldi still selling; Biogen's tecfidera launch 'going well.' May 9, 2014. Available at: http://blogs.barrons.com/stockstowatchtoday/2014/05/09/gilead-sciences-sovaldi-still-selling-biogens-tecfidera-launch-going-well/. (Accessed on 2014 May 12)
4. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013 Apr;57(4):1333-42. doi: 10.1002/hep.26141.
5. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct acting antivirals, for use in large-scale treatment access programs in developing countries. Clin Infect Dis. 2014 Apr;58(7):928–36. doi: 10.1093/cid/ciu012.
6. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011;17(2):107–15.
7. Negro F, Alberti A. The global health burden of hepatitis C virus infection. Liver Int. 2011;Suppl 2:1–3.
8. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; April 2014. Available from: http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/. (Accessed 2014 June 3)
9. Hirschler B. WHO joins clamor to make new hepatitis C pills available. Reuters. April 9, 2014. Available at: http://www.reuters.com/article/2014/04/09/health-hepatitis-idUSL6N0MZ47K20140409. (Accessed on 2014 April 16)
10. Callaway E. Hepatitis C drugs not reaching poor. Nature. 2014 Apr 17;508(7496):295–6. doi: 10.1038/508295a.
11. Médecins Sans Frontières. MSF Access Campaign. MSF responds to reports on Gilead pricing for hepatitis C drug sofosbuvir in developing countries. Available at: http://www.msfaccess.org/content/msf-responds-reports-gilead-pricing-hepatitis-c-drug-sofosbuvir-developing-countries. (Accessed on 2014 April 4)
12. Lawitz E, Ghalib R, Rodriguez-Torres, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype-1 prior null-responder/treatment-naive patients (COSMOS study): primary endpoint (SVR-12) results in patients with METAVIR F3-4 (cohort 2) (Abstract 0165). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.
13. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013 Aug 28;310(8):804–11. doi: 10.1001/jama.2013.109309.
14. Ruane PJ, Ain, D, Meshrekey R, et al. Sofosbuvir plus ribavirin, an interferon-free regimen, in the treatment of treatment-naive and treatment-experienced patients with chronic genotype 4 HCV infection (Abstract P1243). Paper presented at 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

15. Sulkowski MS, Rodriguez-Torres M, Lalezari J, et al. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotype 1, 2 and 3 infection in patients co-infected with HIV (PHOTON-1) (Abstract 212). Paper presented at: 64rd Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1–4; Washington, D.C.

16. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al; AI444040 Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014 Jan 16;370(3):211–21. doi: 10.1056/NEJMoa1306218.

17. Sulkowski MS, Jacobson IM, Ghalib R, et al. Once-daily simeprevir (TMC-435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype-1 prior null responders with METAVIR F0-2: COSMOS study subgroup analysis (Abstract 7). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13. London, United Kingdom.

18. Zeuzem S, Dusheiko GM, Salupere R, et al; the VALENCE Investigators. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014 May 22;370(21):1993-2001. doi: 10.1056/NEJMoa1316145.

19. Wu G, Zaman MH. Low-cost tools for diagnosing and monitoring HIV infection in low-resource settings. Bull World Health Organ. 2012 Dec 1;90(12):914–20. doi: 10.2471/BLT.12.102780.

20. Nelson DR, Zeuzem S, Andreone P, et al. Balapiravir plus peginterferon alfa-2a (40KD)/ribavirin in a randomized trial of hepatitis C genotype 1 patients. Ann Hepatol. 2012 Jan–Feb;11(1):15–31.

21. Sofia MJ. Nucleotide prodrugs for HCV therapy. Antivir Chem Chemother. 2011 Aug 23;22(1):23–49. doi: 10.3851/IMP1797.

22. Lawitz E, Ghalib R, Rodriguez-Torres, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype-1 prior null-responder/treatment-naive patients (COSMOS study): primary endpoint (SVR-12) results in patients with METAVIR F3-4 (cohort 2) (Abstract 0165). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

23. Sulkowski MS, Jacobson IM, Ghalib R, et al. Once-daily simeprevir (TMC-435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype-1 prior null responders with METAVIR F0-2: COSMOS study subgroup analysis (Abstract 7). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

24. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C. January 2014. Available at: http://www.hcvguidelines.org. (Accessed on 2014 April 22)

25. European Association for the Study of the Liver (EASL). Recommendations on treatment of hepatitis C. April 2014. Available at: http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C/index.html. (Accessed on 2014 May 2)

26. Bio Trends Research Group. Launch Trends® Sovaldi and Olysio (Hepatitis C Virus) (Wave 2) 2014 (US). May 2014. Available at: http://www.bio-trends.com/Products-and-Services/Report?r=LATRID0214. (Accessed on 2014 May 26)

27. Everson GT, Tran TT, Towner WJ, et al. Safety and efficacy of treatment with interferon-free, ribavirin-free combination of sofosbuvir + GS-5816 in treatment-naive patients with genotypes 1-6 HCV infection (Abstract 111). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

28. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus RBV for hepatitis C. N Engl J Med. 2013 Jan 3;368(1):34–44. doi: http://www.nejm.org/doi/full/10.1056/NEJMoa1208953.

29. Gane EJ, Hyland RH, An D, 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 (Abstract 6). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

30. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 patients without treatment options. N Engl J Med. 2013 May 16;368(20):1867-77. doi: 10.1056/NEJMoa1214854.

31. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878–87.doi: 10.1056/NEJMoa1214853.

32. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir in combination with PegIFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment-experienced patients with and without compensated cirrhosis: results from the LONESTAR-2 Study (Abstract LB-4). Paper presented at: 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1–14. Washington, D.C.

33. Dieterich D, Rockstroh J, Orkin C, et al. Simeprevir (TMC-435) plus peginterferon/ribavirin in patients co-infected with HCV genotype-1 and HIV-1: primary analysis of the C212 study (Abstract LBPS9/5). Paper presented at: 14th European AIDS Conference; 2013 October 16–19: Brussels, Belgium.

34. Rockstroh JK, Nelson M, Soriano V, et al; on behalf of the STARTVerso 4 Study Team. STARTVerso 4 phase III trial of faldaprevir plus pegylated interferon α-2a and ribavirin in patients with HIV and HCV genotype-1 co-infection (Abstract 1066). Paper presented at: 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1–14. Washington, D.C.

35. Sulkowski M, Pol S, Mallolas J, et al.; P05411 study investigators. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. Lancet Infect Dis. 2013 Jul;13(7):597–605. doi: 10.1016/S1473-3099(13)70149-X.

36. Sulkowski MS, Sherman KE, Dieterich DT, et al. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. Ann Intern Med. 2013 Jul 16;159(2):86–96. doi: 10.7326/0003-4819-159-2-201307160-00654.

37. Osinusi A, Townsend K, Nelson A, et al. Use of sofosbuvir/ledipasvir fixed dose combination for treatment of HCV genotype-1 in patients coinfected with HIV (Abstract 14). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

38. Sulkowski MS, Mallolas J, Bourliere M, et al. Efficacy and safety of the all-oral regimen, MK-5172/MK-8742 +/- RBV for 12 weeks in G1 HIV/HCV coinfected patients: the C-WORTHY Study (Abstract 63). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

39. Centers for Disease Control and Prevention. National Center for HIV/AIDS, Viral Hepatitis, STD & TB Prevention. Division of Viral Hepatitis. Viral Hepatitis Surveillance. United States, 2011. Available at: http://www.cdc.gov/hepatitis/Statistics/2011Surveillance/PDFs/2011HepSurveillanceRpt.pdf. (Accessed 2013 December 12)

40. Pearlman BL. Hepatitis C virus infection in African Americans. Clin Infect Dis. 2006 Jan 1;42(1):82–91.

41. Aalaei-Andabili SH, Behnava B, Salimi S, Sharafi H, Alavian SM. Mysterious linkages between hepatitis C virus genotypes, interleukin-28B genotypes and viral clearance – a meta-analysis. Hepat Mon. 2014 Mar 2;14(3):e15895. doi: 10.5812/hepatmon.15895.

42. Sloane D, Chen H, Howell C. Racial disparity in primary hepatocellular carcinoma: tumor stage at presentation, surgical treatment and survival. J Natl Med Assoc. 2006 Dec;98(12):1934–9.

43. Wong RJ, Ahmed A. Combination of racial/ethnic and etiology/disease-specific factors are associated with lower survival following liver transplantation in african americans: an analysis from UNOS/OPTN database. Clin Transplant. 2014 Apr 21. doi: 10.1111/ctr.12374.

44. U.S. Department of Health and Human Services Office of Minority Health. Hepatitis and Hispanic Americans. Available at: http://minorityhealth.hhs.gov/templates/content.aspx?lvl=3&lvlid=541&ID=6496. (Accessed on 2013 December 1).

45. Rodriguez-Torres M. Latinos and chronic hepatitis C: a singular population. Clin Gastroenterol Hepatol. 2008 May;6(5):484–90. doi: 10.1016/j.cgh.2008.02.036.

46. Afdhal N, Zeuzem S, Kwo P, et al.; the ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014 May 15;370(20):1889–98. doi: 10.1056/NEJMoa1402454.

47. Afdhal N, Reddy KR, Nelson DR, et al.; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483–93. doi: 10.1056/NEJMoa1316366.

48. Andreone P, Colombo MG, Enejosa JV, et al.; on behalf of the PEARL-II investigators. PEARL-II: randomized phase 3 trial of interferon-free, 12-week regimen of ABT-450/r/ABT-267, ABT-333 with or without ribavirin in hepatitis C virus, genotype 1b-infected, treatment-experienced patients (Abstract Su1061). Paper presented at: Digestive Disease Week 2014; 2014 May 3–6; Chicago, IL.

49. Everson GT, Thuluvath PI, Lawitz E, et al. All-oral combination of daclatasvir, asunaprevir and BMS-791325 for HCV genotype 1 infection (Abstract 52). Paper presented at: 21st Conference on Retroviruses and Opportunistic Infections; 2014 March 3–6; Boston, MA.

50. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1594–603. doi: 10.1056/NEJMoa1315722.

51. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014 May 22;370(21):1983–92. doi: 10.1056/NEJMoa1402338.

52. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients who relapsed after previous therapy: a phase 3 trial. Gastroenterology. 2014 Jun;146(7):1669–79.e3. doi: 10.1053/j.gastro.2014.02.051.

53. Gane EJ, Ben Ari Z, Mollison L, et al. Efficacy and safety of MK-5172 + ribavirin in treatment-naive patients with hepatitis C virus genotype1 infection: final results of the C-SPIRIT study (Abstract 1233). Paper presented at 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

54. Jacobson IM, Asselah T, Ferenci P, et al; on behalf of the STARTVerso Study Group. A randomized, double-blind, placebo-controlled phase III trial of faldaprevir in combination with pegylated interferon α-2a and ribavirin in treatment-experienced patients with chronic HCV genotype-1 infection (Abstract 1100). Paper presented at: 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1–14; Washington, D.C.

55. Jacobson I, Dore GJ, Foster GR, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naïve patients: results from QUEST-1 a phase III trial (Abstract 1425). Paper presented at 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

56. Jensen D, Asselah T, Dieterich D, et al; on behalf of the STARTVerso1 and STARTVerso2 Study Groups. A pooled analysis of two randomized, double-blind placebo-controlled phase III trials (STARTVerso 1 and 2) of faldaprevir plus pegylated interferon α-2a and ribavirin in treatment-naive patients with chronic hepatitis C genotype-1 infection (Abstract 1088). Paper presented at: 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1–14. Washington, D.C.

57. Kohli A, Sims Z, Marti M, et al. Combination oral, hepatitis C antiviral therapy for 6 or 12 weeks: results of the SYNERGY trial (Abstract 27 LB). Paper presented at: 21st Conference on Retroviruses and Opportunistic Infections; 2014 March 3–6; Boston, MA.

58. Kowdley KV, Gordon SC, Reddy R, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014 May 15;370(20):1879–88. doi: 10.1056/NEJMoa1402355.

59. Lawitz E, Vierling J, Murillo A, et al. High efficacy and safety of the all-oral combination regimen, MK-5172/MK-8742 ± RBV for 12 weeks in HCV genotype 1 infected patients: the C-WORTHY study (Abstract 76). Paper presented at 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-14. Washington, DC.

60. Lawitz E, Hezode C, Varunok P, et al. Interferon- and ribavirin- free regimen of ABT-450/r + ABT-267 in HCV genotype 1b-infected treatment-naive patients and prior null responders (Abstract 74). Paper presented at: 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1–14. Washington, D.C.

61. Lawitz E, Hezode C, Gane E, et al. Efficacy and safety of MK-5172 and MK-8742 ± ribavirin in hepatitis C genotype 1 infected patients with cirrhosis or previous null response: the C-WORTHY Study (Abstract 61). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

62. Manns M, Marcellin P, Poordad F, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naive patients: results from QUEST-2 a phase III trial (Abstract 1413). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

63. Manns MP, Pol S, Jacobson IM, et al. All-oral dual therapy with daclatasvir and asunaprevir in patients with HCV genotype 1b infection: phase 3 HALLMARK-DUAL study results (Abstract 166). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

64. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014 May 22;370(21):1973–82. doi: 10.1056/NEJMoa1402869.

65. Gane EJ, Lawitz E, Rodriguez-Torres M, et al. Phase 3 randomized controlled trial of all-oral treatment with sofosbuvir + RBV for 12 weeks compared to 24 weeks of peg + RBV in treatment-naive GT2/3 HCV-infected patients (FISSION) (Abstract 5). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

66. Gane EJ, Ben Ari Z, Mollison L, et al. Efficacy and safety of MK-5172 + ribavirin in treatment-naive patients with hepatitis C virus genotype1 infection: final results of the C-SPIRIT study (Abstract 1233). Paper presented at: 49th Annual Meeting of the European Association for the Study of Liver Diseases Meeting; 2014 April 9–13; London, United Kingdom.

67. Nelson D, Feld J, Kowdley KV, et al. All-oral therapy with sofosbuvir + plus RBV for 12 or 16 weeks in treatment experienced GT2/3 HCV-infected patients: results of the phase 3 FUSION trial (Abstract 6). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28. Amsterdam, the Netherlands.

68. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005 Sep;5(9):558–67.

69. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011 Aug 13;378(9791):571–83. doi: 10.1016/S0140-6736(11)61097-0.

70. Harris M, Rhodes T. Hepatitis C treatment access and uptake for people who inject drugs: a review mapping the role of social factors. Harm Reduct J. 2013 May 7;10:7. doi: 10.1186/1477-7517-10-7.

71. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis._Clin Infect Dis. 2013 Aug;57 Suppl 2:S80–9. doi: 10.1093/cid/cit306.

72. Martin NK, Vickerman P, Grebely J, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatology. 2013 Nov;58(5):1598–609. doi: 10.1002/hep.26431.

73. El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C World J Gastroenterol. 2013 Nov 28;19(44):7880–8. doi: 10.3748/wjg.v19.i44.7880.

74. Polis CB, Shah SN, Johnson KE, Gupta A. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. Clin Infect Dis. 2007 Apr 15;44(8):1123–31.

75. Jonas MM, Balistreri W, Gonzalez-Peralta RP, et al. Pegylated interferon for chronic hepatitis C in children affects growth and body composition: results from the pediatric study of hepatitis C (PEDS-C) trial. Hepatology. 2012 Aug;56(2):523–31. doi: 10.1002/hep.25690.