Hepatitis C Drug Development Catapults Onward

By Tracy Swan

Thanks to Jules Levin

The pace of, and progress in, hepatitis C virus (HCV) drug development are astonishing. In April 2011, proof-of-concept for safe, effective, peginterferon-free HCV treatment was announced. Since then, numerous trials have confirmed that hepatitis C virus is curable with direct-acting antivirals (DAAs), regardless of HCV treatment history, cirrhosis, or host genotype.

Over the past 24 months, duration of treatment and assessment of posttreatment outcome have been dramatically abbreviated. Old-school, 48-week regimens with SVR-24 are gone. Now, duration of treatment is usually 12 to 24 weeks, and SVR-12 is the endpoint that is commonly used as a surrogate for cure.[1] Interim data are now available within a few months after trials start. This acceleration in, and rapid evolution of, HCV drug development has left some drugs behind: they are shackled to lumbering development programs, such as the strategy being used in many phase III trials—adding a DAA to 24 or 48 weeks of response-guided therapy with peginterferon (PEG-IFN) and ribavirin (RBV). This approach is likely to have limited clinical relevance, given the rapid development of peginterferon-sparing and peginterferon-free regimens.

The confluence of a robust HCV drug pipeline, shortened regimens, and posttreatment follow-up are extraordinary. The new FDA breakthrough therapy designation may speed things up as well. By the end of 2014, DAAs from four different classes and fixed-dose combinations (FDCs) are likely to be approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), offering the potential for off-label mixing and matching.

Table 1. HCV Treatments in Phase II and Phase III

Agent	Dosing	Sponsor	Status
Nucleoside/nucleotide polymerase inhibitors			
sofosbuvir (GS-7977)	Once-daily	Gilead Sciences	Phase III
mericitabine (RG7128)	Twice-daily	Hoffmann-La Roche/Genentech	Phase III
VX-135	Once-daily	Vertex Pharmaceuticals	Phase II
Non-nucleoside polymerase inhibitors			
ABT-333	Twice-daily	AbbVie	Phase III
BI 207127	Twice-daily	Boehringer Ingelheim	Phase III
GS-9669	Once-daily	Gilead Sciences	Phase II
setrobuvir (ANA-595)	Twice-daily	Hoffmann-La Roche/Genentech	Phase II
VX-222	Twice-daily	Vertex Pharmaceuticals	Phase II
TMC647055	Twice-daily	Janssen	Phase I/II
NS5A inhibitors			
ABT-267	Once-daily	AbbVie	Phase III
daclatasvir (BMS-790052)	Once-daily	Bristol-Myers Squibb	Phase III
ledipasvir (GS-5885)	Once-daily	Gilead Sciences	Phase III
ACH-3102	Once-daily	Achillion Pharmaceuticals	Phase II
GS-5816	Once-daily	Gilead Sciences	Phase II
GSK2336805	Once-daily	GlaxoSmithKline	Phase II
IDX719	Once-daily	Idenix Pharmaceuticals	Phase II
MK-8742	Once-daily	Merck	Phase I/II
Protease inhibitors			
ABT-450/r (ritonavir-boosted)	Once-daily	AbbVie	Phase III
asunaprevir (BMS-650032)	Twice-daily	Bristol-Myers Squibb	Phase III
faldaprevir (BI 201335)	Once-daily	Boehringer Ingelheim	Phase III
simeprevir (TMC435)	Once-daily	Janssen/Tibotec/Medivir	Phase III
danoprevir/r (RG7227) (ritonavir-boosted)	Twice-daily	Hoffmann-La Roche/Genentech	Phase II
GS-9451	Once-daily	Gilead Sciences	Phase II
MK-5172	Once-daily	Merck	Phase II
sovaprevir (ACH-1625)	Once-daily	Achillion Pharmaceuticals	Phase II
MicroRNA-targeting			
miravirsen	Once-weekly	Santaris Pharma A/S	Phase II
Fixed-dose combinations			
ABT-267/ABT-450/r	Once-daily	AbbVie	Phase III
sofosbuvir/ledipasvir	Once-daily	Gilead Sciences	Phase III

To Market, To Market

On March 28, 2013, Janssen Research and Development (R&D) and Medivir AB submitted an application to the U.S. Food and Drug Administration (FDA) for approval of simeprevir, a once-daily protease inhibitor used with peginterferon and ribavirin in HCV genotype 1.

On April 8, 2013, Gilead Sciences submitted an application to the FDA for approval of sofosbuvir, an HCV nucleotide polymerase inhibitor, for use with ribavirin in HCV genotypes 2 and 3, and in combination with peginterferon and ribavirin for HCV genotypes 1,4, 5, and 6.

The Best Combinations

HCV drug development has evolved from single drugs to complete regimens (see tables 2 and 3). But identifying and constructing optimal HCV treatment regimens is not straightforward due to differences in patient populations and individual drug characteristics. An ideal regimen is not always comprised of best-in-class drugs (even if one company owns all of them). Some drugs may not be appropriate for co-formulation or coadministration due to differences in dosing schedule, food and refrigeration requirements, resistance profile, activity against certain HCV genotypes and subtypes, side effects, and contraindications. Drug-drug interactions (DDIs) with other medications commonly used by people with hepatitis C—and possible interactions between drugs in the regimen—must be avoided to reduce the risk of worsened side effects from overdosing, or treatment failure from underdosing. Each drug needs to be good enough to get the job done without adding to side effects, safety concerns, monitoring requirements, or complexity of administering and undergoing HCV treatment.

Table 2. Interferon-Free Regimens in Development for HCV Genotype 1

Regimen	Status/ Sponsor	Population	Duration
ABT-267 + ABT-333 + ABT-450/r + RBV	Phase II AbbVie	Posttransplant (no prior DAA)	24 weeks
ABT-267 + ABT-450/r +/− RBV ABT-267 + ABT-333 + ABT-450/r +/− RBV ABT-333 + ABT-450/r +/− RBV	Phase II AbbVie	Treatment-naive or null responders (no prior DAA); non-cirrhotic	8 to 24 weeks
ABT-267 + ABT-450/r +/− RBV	Phase II AbbVie	Treatment-naive or treatment-experienced (no prior DAA); non-cirrhotic; HCV genotype 1b	12 weeks
FDC: ABT-267/ABT-450/r + ABT-333 +/− RBV	Phase III AbbVie	Treatment-naive; non-cirrhotic; HCV genotype 1b	12 weeks
FDC: ABT-267/ABT-450/r + ABT-333 + RBV	Phase III AbbVie	Treatment-experienced (no prior DAA); non-cirrhotic	12 weeks
FDC: ABT-267/ABT-450/r + ABT-333 + RBV	Phase III AbbVie	Treatment-naive; non-cirrhotic	12 weeks
FDC: ABT-267/ABT-450/r + ABT-333 + RBV	Phase III AbbVie	Treatment-naive or treatment-experienced (no prior DAA); compensated cirrhosis	12 or 24 weeks
sovaprevir + ACH-3102	Phase II Achillion	Treatment-naive	12 weeks
asunaprevir + daclatasvir + BMS-791325	Phase II BMS	Treatment-naive or non and null responders (no prior DAA)	12 or 24 weeks
daclatasvir + sofosbuvir +/− RBV	Phase II BMS/ Pharmasset	Treatment-naive; non-cirrhotic	12 or 24 weeks
daclatasvir + simeprevir +/− RBV + PEG-IFN/RBV (if necessary)	Phase II BMS/Janssen	Treatment-naive or null responders (no prior DAA)	12 or 24 weeks
asunaprevir + daclatasvir + PEG-IFN/RBV (if necessary)	Phase III BMS	Treatment-naive, interferon-ineligible or -intolerant; partial and null responders (no prior DAA); HCV genotype 1b	24 weeks
faldaprevir + BI 207127 + RBV	Phase III Boehringer Ingelheim	Treatment-naive; non-cirrhotic; HCV genotype 1b	16 or 24 weeks
sofosbuvir + GS-5816	Phase II Gilead	Treatment-naive; non-cirrhotic	12 weeks
FDC: sofosbuvir/ledipasvir or sofosbuvir + GS-9669	Phase II Gilead	Treatment-naive or null responders (no prior DAA)	12 weeks
FDC: sofosbuvir/ledipasvir +/− RBV	Phase II Gilead	Treatment-naive	8 or 12 weeks

Regimen	Status/ Sponsor	Population	Duration
sofosbuvir + RBV	Phase II Gilead	No prior treatment with HCV nucleoside/tide; portal hypertension with or without hepatic decompensation	48 weeks
		Posttransplant	24 weeks
		Pretransplant (for hepatocellular carcinoma)	24 weeks
ledipasvir + GS-9451 +/– tegobuvir +/– RBV	Phase II Gilead	Treatment-naive; non-cirrhotic	12 or 24 weeks
		Interferon-ineligible or -intolerant; non-cirrhotic	24 weeks
FDC: sofosbuvir/ledipasvir +/– RBV	Phase III Gilead	Treatment-naive or treatment-experienced (including prior use of an HCV protease inhibitor)	12 or 24 weeks
danoprevir/r + mericitabine +/– RBV + PEG-IFN/RBV in the no-RBV arm (if necessary)	Phase II Hoffmann-La Roche	Treatment-naive; no advanced fibrosis or cirrhosis	24 weeks +/– 24-week PEG-IFN/RBV
danoprevir/r + setrobuvir +/– mericitabine + RBV	Phase II Hoffmann-La Roche	Treatment-naive and treatment-experienced (PEG-IFN/RBV only); non-cirrhotic	12 weeks
sofosbuvir + simeprevir +/– RBV	Phase II Janssen/ Gilead	Null responders; mild/moderate liver damage	12 or 24 weeks
		Treatment-naive and null responders; bridging fibrosis/ cirrhosis	
simeprevir + TMC647055/r +/– RBV + PEG-IFN/RBV (if necessary)	Phase II Janssen	Treatment-naive, relapsers, or null responders; HCV genotype 1a and 1b	12 weeks +/– 12-week PEG-IFN/RBV
MK-5172 +/– RBV	Phase II Merck	Treatment-naive; non-cirrhotic; IL28B CC genotype only	12 or 24 weeks
MK-5172 + MK-8742 + RBV	Phase II Merck	Treatment-naive; absence of advanced fibrosis or cirrhosis	12 weeks
miravirsen	Phase II Santaris	Null responders (no prior DAA)	12 weeks
VX-135 + RBV	Phase II Vertex	Treatment-naive; non-cirrhotic	12 weeks
telaprevir + VX-222 + RBV	Phase II Vertex	Treatment-naive	12 or 16 weeks

Source: www.clinicaltrials.gov

Table 3. Interferon-Free Regimens in Development for HCV Genotypes 2, 3, & 4

Regimen	Status/ Sponsor	Population	Duration
ABT-267 + ABT-450/r +/− RBV	Phase II AbbVie	Treatment-naive; HCV genotypes 2 & 3	Not Specified
FDC: ABT-267/ABT-450/r + ABT-333 + RBV	Phase II AbbVie	Treatment-naive and treatment-experienced (no prior DAA)	12 weeks
asunaprevir + daclatasvir + BMS-791325	Phase II BMS	Treatment-naive; HCV genotype 4	12 or 24 weeks
daclatasvir + sofosbuvir +/− RBV	Phase II BMS/ Pharmas-set	Treatment-naive; non-cirrhotic; HCV genotypes 2 & 3	24 weeks
sofosbuvir + GS-5816	Phase II Gilead	Treatment-naive, non-cirrhotic; HCV genotypes 2, 3, 4, 5, & 6	12 weeks
FDC: sofosbuvir/ledipasvir or sofosbuvir + GS-9669	Phase II Gilead	Treatment-naive or null responders (no prior DAA); HCV genotype 4	12 weeks
FDC: sofosbuvir/ledipasvir +/− RBV	Phase II Gilead	Treatment-naive; HCV genotype 3	12 weeks
sofosbuvir + RBV	Phase II Gilead	Interferon-ineligible or -intolerant; HCV genotypes 2 & 3	12 weeks
sofosbuvir + RBV	Phase II Gilead	All genotypes; no prior treatment with HCV nucleoside/tide; portal hypertension with or without hepatic decompensation	48 weeks
		Posttransplant	24 weeks
		Pretransplant (for hepatocellular carcinoma)	24 weeks
sofosbuvir + RBV	Phase II Gilead	Treatment-naive and treatment-experienced Egyptian adults; HCV genotype 4	12 or 24 weeks
sofosbuvir + RBV	Phase III Gilead	Prior sofosbuvir study participants; HCV genotypes 2 & 3	12 weeks
		Treatment-naive; interferon-intolerant, -ineligible, or -unwilling	12 weeks
		Treatment-experienced (no prior DAA); HCV genotypes 2 & 3	12 or 16 weeks

Source: www.clinicaltrials.gov

Financial considerations play a significant role in HCV drug development. Competition for market share is fierce, since experts estimate that the HCV market in the "big 7" (Japan, the United Kingdom, Germany, France, Italy, Spain, and the United States) will reach US$14 billion to US$20 billion by 2018. Most pharmaceutical companies are developing in-house combinations to avoid sharing the jackpot. As a result, only three trials have combined DAAs from different sponsors. Sofosbuvir (Gilead's nucleotide polymerase inhibitor) has been paired with daclatasvir, an NS5A inhibitor from Bristol-Myers Squibb (BMS), and simeprevir (an HCV protease inhibitor from Janssen).

Sofosbuvir and daclatasvir have been tested in a phase IIa trial, with or without RBV—and results were spectacular. Cure rates ranged from 88 percent to 100 percent after 12 or 24 weeks of treatment, regardless of treatment history, ribavirin use, HCV genotype or subtype, IL28B genotype, or treatment duration. The study included 170 non-cirrhotic, treatment-naive participants with HCV genotypes 1, 2, and 3, and 41 treatment-experienced (with an HCV protease inhibitor-based regimen) participants with HCV genotype 1. The regimen was safe and tolerable.[2,3] Unfortunately, Gilead is unwilling to continue this clinical collaboration because they are developing their own NS5A inhibitor, ledipasvir, in a fixed-dose combination (FDC) with sofosbuvir (see Twinkle, Twinkle, Little (Lone) Star on page 177).

COSMOS, a 167-person, phase IIa trial, is pairing simeprevir and sofosbuvir for 12 or 24 weeks, with or without ribavirin. COSMOS includes two cohorts of null responders with HCV genotype 1 (people with very mild to moderate liver scarring versus people with extensive liver scarring and cirrhosis). Although most of cohort 1 had poor prognostic factors (IL28B non-CC genotype and HCV genotype 1a), early results were stellar: at posttreatment week 8 (referred to as SVR-8), 96 percent (or 26 of 27 people) in the sofosbuvir/simeprevir/RBV arm, and 92 percent (or 13 of 14 people) in the sofosbuvir/simeprevir arm maintained undetectable HCV RNA. There were no discontinuations, but two relapses occurred (one in each arm). So far, 24 people have been followed until posttreatment week 12 (SVR-12), and 100 percent remain undetectable. The regimen was safe and tolerable; the second cohort (87 people with serious liver damage) was fully enrolled as of March of 2013.[4] It is likely that Gilead's partnership with Janssen will be short-lived, regardless of the final results from COSMOS.

Simeprevir and daclatasvir are being tested, with or without RBV, for 12 or 24 weeks (plus an optional extra 24 weeks of peginterferon/ribavirin if needed), in an ongoing phase II trial of 180 treatment-naive and prior null responders with HCV genotype 1, including people with cirrhosis.

Off-label use of drugs on similar regulatory timelines (such as simeprevir and sofosbuvir) may be possible (although the cost may be prohibitive). Without larger phase III trials, securing reimbursement for mix-and-match regimens may be a challenge, although activists—and drug makers—are pressing for access.

Cross-company Trials

Some companies have chosen a collaborative approach to stay in the game.

- Boehringer Ingelheim and Presidio will collaborate on a phase IIa trial focusing on HCV genotype 1a, combining faldaprevir (an HCV protease inhibitor), BI 207127 (a non-nucleoside polymerase inhibitor), and PPI-668 (an NS5A inhibitor), with or without RBV.[5]
- Bristol-Myers Squibb and Merck will collaborate on a phase II trial pairing daclatasvir (an NS5A inhibitor) with MK-5172 (an HCV protease inhibitor) in genotype 1.[6]
- Janssen and Idenix will collaborate on a phase IIa trial of simeprevir and IDX719 (an NS5A inhibitor), with or without RBV.[7]
- Janssen and Vertex will collaborate on a phase II trial pairing simeprevir with VX-135 (a nucleotide polymerase inhibitor).[8]
- Vertex and BMS will collaborate on a pair of phase II trials pairing VX-135 with daclatasvir (an NS5A inhibitor), initially in treatment-naive people with HCV genotype 1, then in treatment-naive people with HCV genotypes 1, 2, and 3. Vertex plans to conduct "co-formulation activities" as part of the agreement.[9]
- Vertex and GlaxoSmithKline will collaborate on a phase II trial of VX-135 with GSK2336805 (an NS5A inhibitor), with or without RBV.[10]

Next in Line: Simeprevir, Faldaprevir, and Sofosbuvir

Simeprevir, a once-daily HCV protease inhibitor, is being developed in peginterferon-based and peginterferon-free regimens. Although simeprevir's approval hinges on trials with peginterferon, it is likely to be used in different ways as peginterferon phases out. Simeprevir is currently in trials with TMC647055, a ritonavir-boosted non-nucleoside polymerase inhibitor, with or without ribavirin, sofosbuvir (with or without ribavirin), and daclatasvir (with or without ribavirin, or PEG-IFN and ribavirin "rescue"). Additional studies are planned with VX-135 (a nucleotide polymerase inhibitor) and IDX719 (an NS5A inhibitor) plus TMC 647055.

QUEST-2, a trial of 391 treatment-naive people with HCV genotype 1, compared response-guided therapy (12 weeks of once-daily simeprevir plus PEG-IFN alfa-2a or alfa-2b and RBV, followed by 12 or 36 weeks of PEG-IFN and RBV to PEG-IFN and RBV alone). More than 90 percent (235 of 257) were eligible for shortened treatment, and 86 percent of them (202 of 235) were cured. Of the 8 percent who were not eligible for shortened treatment, 31 percent (7 of 22) were cured, leading to an overall cure rate of 81 percent (vs. 50% for PEG-IFN and RBV). With simeprevir-based treatment, cure rates were higher in people with the IL28B CC genotype (96%) than CT (80%) or TT (57%), although SVR did not differ by HCV subtype. People with little or no liver damage were more likely to be cured (84%) than people with widespread fibrosis and cirrhosis, although cure rates for this group were high (66% and 64%). Most treatment failures and relapses were associated with emergent drug resistance; primarily the R155K mutation, either alone or with additional mutations in position 80 or 168, in HCV genotype 1a, whereas in HCV genotype 1b, treatment failure was associated with either the D168V mutation or Q80R plus D168E. Of note, SVR rates were higher among people treated with peginterferon alfa-2a, whether they received simeprevir or placebo.

Simeprevir did not worsen side effects during the first 12 weeks of treatment, with the exception of (mostly) mild rash and photosensitivity. Simeprevir was associated with transient increases in bilirubin. Otherwise, there were no significant differences in mild, moderate, or serious adverse events.[11]

Results from QUEST-1, a trial in 394 treatment-naive people with HCV genotype 1, were remarkably similar to those reported from QUEST-2. The overall SVR rate was 80 percent (simeprevir arm) versus 50 percent for peginterferon, ribavirin, and placebo. Of the 85 percent in the simeprevir arm who were eligible for shorter treatment, 91 percent were cured. As in QUEST-2, baseline and emergent drug resistance were associated with unsuccessful treatment; this occurred more in HCV genotype 1a than HCV genotype 1b.The most common adverse events in both treatment arms were fatigue, pruritus (itching), and headache.[12]

Simeprevir is being studied in HCV genotype 4, null and partial responders, and HIV/HCV coinfection (treatment-naive and treatment-experienced). To date, 250 people with compensated cirrhosis (Child-Pugh class A only) have been in trials of simeprevir; dose adjustments may be needed in people with Child-Pugh class B or C.[13]

Faldaprevir, a once-daily HCV protease inhibitor, is nearing the finish line. STARTVerso 1, a phase III trial in 652 treatment-naive people with HCV genotype 1, compared different doses (120 mg vs. 240 mg) of faldaprevir-based response-guided therapy to PEG-IFN/RBV and ribavirin plus placebo. The trial was conducted in Europe and Japan (where body mass index is lower, and the IL28B CC genotype is more common—factors that increase likelihood of cure). Early responders were eligible for shorter treatment; 88 percent met the criteria and most (86–89%) were cured, regardless of faldaprevir dose. Of note, cure rates were higher in people with undetectable HCV RNA at week 4 versus those with a viral load of ≤25 copies IU/mL. With the lower dose of faldaprevir, elevated bilirubin, rash, and gastrointestinal side effects were less frequent.[14]

Faldaprevir is also being studied in treatment-experienced people, and in HIV/HCV coinfection. An all-oral regimen (faldaprevir, BI 207127, and ribavirin) is being developed in HCV genotype 1b, and a trial combining faldaprevir, BI 207127, and PPI-668, with or without ribavirin, is planned.

Without a PEG to Stand on: The Sofosbuvir Saga Goes on

Sofosbuvir offered the promise of highly effective, peginterferon-free, oral, short-course treatment for everyone. Small trials reported 100 percent cure rates in genotypes 2 and 3, and 84 percent in genotype 1 after 12 weeks of sofosbuvir and ribavirin. But rates plummeted when this regimen moved into groups with difficult-to-treat characteristics. Only 1 of 9 null responders with HCV genotype 1 was cured by 12 weeks of sofosbuvir and ribavirin.[15] In the SPARE trial, cure rates ranged from 68 percent to 48 percent after 24 weeks of sofosbuvir and weight-based or low-dose ribavirin (600 mg). Most SPARE participants were African American, and had non-CC genotypes, HCV genotype 1a, and high hepatitis C viral load; almost 30 percent had widespread liver scarring.[16]

Biting the (Magic) Bullet

Until peginterferon-free regimens are available for HCV genotype 1, the best option for treatment-naive people may be 12 weeks of sofosbuvir plus PEG-IFN and RBV: this regimen cured 90 percent (48 of 54) in the phase II ATOMIC trial, and 89 percent (260 of 292) in the phase III NEUTRINO trial (a subset of NEUTRINO participants had cirrhosis; 80 percent [44 of 55] were cured).[17,18]

Twinkle, Twinkle, Little (Lone) Star

Sofosbuvir-based, peginterferon-free treatment is on the way for HCV genotype 1. Swapping out peginterferon for a DAA seems to do the trick: in ELECTRON, 100 percent of 25 treatment-naive and 10 null-responder participants were cured by 12 weeks of sofosbuvir, ledipasvir, and ribavirin.[19] Sofosbuvir and ledipasvir have been co-formulated into a fixed-dose combination (FDC).

Ribavirin may be next to go, based on interim results from LONESTAR, a 100-person, phase II trial (60 treatment-naive; 40 treatment-experienced with an HCV protease inhibitor–based regimen). LONESTAR compared

8 weeks of the FDC, with and without ribavirin, to 12 weeks of the FDC, with or without ribavirin. In the treatment-naive cohort, 100 percent of the 19 people treated for 12 weeks maintained undetectable HCV RNA 4 weeks after finishing treatment (SVR-4); 40 of 41 participants in the 8-week arm maintained undetectable HCV RNA 8 weeks after treatment completion (SVR-8). In the treatment-experienced cohort, 95 percent achieved SVR-4.[20]

The FDC is currently in phase III trials. It is being studied with and without RBV in treatment-naive people with genotypes 1, 3, and 4 and treatment-experienced people with HCV genotype 1 for durations ranging from 8 to 24 weeks.

AbbVie: All Hands on Deck

AbbVie's powerhouse regimen (ABT-450/r, a boosted HCV protease inhibitor co-formulated with ABT-267, an NS5A inhibitor, plus ABT-333 [a non-nucleoside polymerase inhibitor] and ribavirin) has yielded almost universal cure rates in clinical trials among treatment-naive and null-responder participants, regardless of HCV subtype or IL28B genotype; over 90 percent were cured after 12 weeks of treatment.[21] The regimen is now being studied in people with compensated cirrhosis; a trial in HIV/HCV coinfection is expected in mid-2013.

Bristol-Myers Squibb: All In!

Bristol-Myers Squibb (BMS) is developing a three-drug, ribavirin-free, in-house combination for HCV genotype 1: daclatasvir plus asunaprevir (an HCV protease inhibitor) and BMS 791325 (a non-nucleoside polymerase inhibitor). So far, SVR rates have been close to 100 percent, and the regimen appears safe and tolerable. A phase II trial in both treatment-naive and null-responder participants with HCV genotypes 1 or 4 is planned.[22]

Note: Recently reported SVR rates from interferon-free and interferon-sparing trials for HCV genotypes 1, 4, 5, and 6 are available online at: www.pipelinereport.org/2013/hcv/svr-update.

(Genotype) 3 is the new 1

In the peginterferon era, HCV genotypes 2 and 3 were considered "easy to treat" in contrast to HCV genotypes 1 and 4: duration of treatment was shorter (24 vs. 48 weeks) and cure rates higher. Although genotypes 2 and 3 have historically been lumped together, there are differences: cure rates are higher in genotype 2 than genotype 3 (80–90% vs. 60–70%, respectively); hepatic steatosis (a condition that accelerates liver damage) is associated with genotype 3 infection; liver disease progresses more rapidly in genotype 3 than in genotype 2.[23,24]

But when it comes to DAA-based treatment, genotype 3 is an altogether different animal than genotype 2. Results from small DAA trials in genotype 3 created expectations that eradication would be a slam-dunk: cure rates ranged from 88 percent to 100 percent.[2,15] But larger trials of DAA-based regimens in treatment-naive and treatment-experienced participants with HCV genotypes 2 and 3 have consistently reported a disparity in cure rates, favoring genotype 2 (see table 4).

Finding effective regimens for HCV genotype 3 has proven to be a challenge. Options are limited: HCV protease inhibitors (including faldaprevir, simeprevir, and telaprevir) are inactive or have weakened activity (asunaprevir, danoprevir) against genotype 3; only three (ABT-450/r, boceprevir, and MK-5172) are being studied in HCV genotype 3.[25,26,27,28,29] Resistance to NS5A inhibitors has been detected in treatment-naive people with HCV genotype 3, and some are known to have weaker activity against genotype 3.[30,31] In fact, adding daclatasvir to PEG-IFN and RBV produced disappointing results.[32] Non-nucleoside polymerase inhibitors are inactive against genotype 3 (with the possible exception of a lone candidate in early development), leaving only nucleoside and nucleotide polymerase inhibitors (sofosbuvir and mericitabine are active against genotype 3).[33,34]

It is clear that DAA-based treatment for genotype 3—especially in people with cirrhosis—needs to be optimized: extending duration, and adding peginterferon and ribavirin or another DAA with activity against genotype 3 may do the trick.

Table 4. SVR in HCV Genotypes 2 and 3

Study/Drugs	Population/ Size	Genotype	Treatment Arms	SVR
AI444-040 daclatasvir + sofosbuvir +/− RBV Phase II BMS/Gilead	Treatment-naive, non-cirrhotic (N = 44)	Genotypes 2 & 3	24-week, 2-drug (7-day sofosbuvir lead-in, no RBV)	SVR-24: **88%**
			24-week, 2-drug (no RBV)	SVR-24: **100%**
			24-week, 3-drug	SVR-24: **93%**
COMMAND GT 2/3 daclatasvir + PEG-IFN/RBV vs. placebo + PEG-IFN/RBV Phase II BMS	Treatment-naive, 20% cirrhotic (G3 only) (N = 151)	Genotype 2	12-week	SVR-24: **88%**
			16-week	SVR-24: **83%**
			placebo	SVR-24:: **63%**
		Genotype 3	12-week	SVR-24: **69%**
			16-week	SVR-24: **70%**
			placebo	SVR-24: **59%**
ELECTRON sofosbuvir + RBV + 0, 4, 8, or 12 weeks of PEG-IFN vs. sofosbuvir monotherapy Phase II Gilead	Treatment-naive, non-cirrhotic (N = 60)	Genotypes 2 & 3	8-week, 3-drug	SVR-24: **100%**
			12-week, with 4-week PEG-IFN	SVR-24: **100%**
			12-week, with 8-week PEG-IFN	SVR-24: **100%**
			12-week, 3-drug	SVR-24: **100%**
			12-week, no PEG-IFN	SVR-24: **100%**
			12-week, sofosbuvir only	SVR-24: **60%**
FISSION sofosbuvir + RBV vs. PEG-IFN/RBV Phase III Gilead	Treatment-naive, 20% cirrhotic (N = 499)	Genotype 2	12-week sofosbuvir + RBV	SVR-12: **97%** Cirrhotic: **91%** Non-cirrhotic: **98%**
			24-week PEG-IFN/RBV	SVR-12: **78%** Cirrhotic: **62%** Non-cirrhotic: **82%**
		Genotype 3	12-week sofosbuvir + RBV	SVR-12: **56%** Cirrhotic: **34%** **Non-cirrhotic: 61%**
			24-week PEG-IFN/RBV	SVR-12: **63%** Cirrhotic: **30%** Non-cirrhotic: **71%**

Study/Drugs	Population/ Size	Genotype	Treatment Arms	SVR
FUSION sofosbuvir + RBV Phase III Gilead	Treatment-experienced, 34% cirrhotic (N = 201)	Genotype 2	12-week	SVR-12: **86%** Cirrhotic: **60%** Non-cirrhotic: **96%**
			16-week	SVR-12: **94%** Cirrhotic: **78%** Non-cirrhotic: **100%**
		Genotype 3	12-week	SVR-12: **30%** Cirrhotic: **19%** Non-cirrhotic: **37%**
			16-week	SVR-12: **62%** Cirrhotic: **61%** Non-cirrhotic: **63%**
POSITRON sofosbuvir + RBV Phase III Gilead	Treatment naive, interferon-ineligible, -intolerant, and -unwilling; 15% cirrhotic (N = 207)	Genotype 2	12-week	SVR-12: **93%** Cirrhotic: **94%** Non-cirrhotic: **92%**
		Genotype 3	12-week	SVR-12: **61%** Cirrhotic: **21%** Non-cirrhotic: **68%**
PROTON sofosbuvir + PEG-IFN/RBV Phase II Gilead	Treatment-naive, non-cirrhotic (N = 25)	Genotypes 2 and 3	12-week	SVR-12: **92%**

Sources:

Dore GJ, Lawitz E, Hézode C, et al. Daclatasvir combined with peginterferon alfa-2a and ribavirin for 12 or 16 weeks in patients with hepatitis C virus genotype 2 or 3 infection: COMMAND GT 2/3 study (Abstract 1418). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

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

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013 Apr 23. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1214854. (Accessed 2013 May 3)

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 Apr 23. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1214853. (Accessed 2013 May 3)

Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. Lancet Infect Dis. 2013 May;13(5):401–8. doi: 10.1016/S1473-3099(13)70033-1.

Cirrhosis: From Frontier to Proving Ground

Demonstrating that DAAs were effective in null responders was the first proving ground for peginterferon-sparing and peginterferon-free regimens. But cirrhosis is clearly the true test: HCV treatment that is safe and effective for people with cirrhosis will work at least as well for everyone else.

DAAs can—and ought to—be studied in people with compensated cirrhosis once adequate pharmacokinetic data in people with renal and/or hepatic impairment and results from critical DDI studies are available, and evidence of safety and efficacy has been established. A phase II trial, SOUND-C, is an example of this proactive approach since it included a subset of 33 people with compensated cirrhosis and reported cure rates in this group as high as 67 percent.[35]

Prioritizing people with more serious liver damage for HCV treatment is both ethical and sensible, given the anticipated king's ransom charged for DAAs and the limited resources to pay for them. This strategy will avert near-term morbidity, transplantation, and mortality from liver disease. Yet patients with advanced liver disease have been underrepresented in, or excluded from, many clinical trials. Drugs are being brought to market with limited data in people with cirrhosis, who are most likely to be treated first. Serious side effects—and fatalities—have been reported from trials of boceprevir- and telaprevir-based regimens in people with compensated cirrhosis.[36] Even without peginterferon, safety issues are paramount for people with advanced liver disease.

Trials in people with compensated cirrhosis provide data to inform pre-approval access for the people who need treatment most. If no safety signals arise, early access programs open to people who are ineligible for clinical trials because they are too sick. The benefits of early access spread beyond people who receive potentially lifesaving treatment. Critical safety data are generated through early access programs to guide widespread use in people with urgent need once drugs are approved.

HIV/HCV Coinfection

HCV coinfection increases AIDS-related, liver-related, and all-cause mortality among people with HIV, despite use of antiretroviral therapy (ART).[37,38] The incidence of HCV-related complications has been rising sharply among HIV/HCV-coinfected people. Since 1996, the incidence of cirrhosis among HIV/HCV-coinfected patients in care at the Veteran's Administration (VA) has risen from 3.5% to 13.2%, and hepatocellular carcinoma from 0.07% to 1.62%— a shocking 23-fold increase.[39]

Clearly, people who are HIV/HCV-coinfected ought to be a priority population for DAA trials, since they are at risk for more rapid HCV progression. Sponsors stand to benefit from supporting these trials, since systems that deliver ART to HIV-positive people could be expanded to include DAAs for both HCV-coinfected and HCV-monoinfected people. But development of peginterferon-free trials has been lagging: as of May 2013, only one peginterferon-free trial (sofosbuvir and ribavirin) was open to HIV/HCV-coinfected people; ongoing trials with simeprevir, faldaprevir, and daclatasvir are peginterferon-based.

But there is welcome news: initial reports that HIV does not appear to be a prognostic factor when a DAA is added to peginterferon and ribavirin have been supported by data from trials of telaprevir-based treatment, as well as interim reports from STARTVerso 4 (faldaprevir-based treatment) and the TMC435-C212 (simeprevir-based treatment) study.[40,41,42]

Faldaprevir plus PEG-IFN/RBV

STARTVerso 4 is an ongoing, 308-person, phase III trial of faldaprevir plus peginterferon and ribavirin in HIV/HCV-coinfected people with HCV genotype 1 who were treatment-naive or relapsers; 17 percent were cirrhotic. The mean CD4 cell count was 545 cells/uL. Participants were randomized (if not on HIV treatment, or raltegravir- or maraviroc-based regimen) to either 120 mg or 240 mg of faldaprevir, or assigned to 120 mg of faldaprevir (for darunavir/r- or atazanavir/r-based-regimens) or 240 mg of faldaprevir (for efavirenz-based regimens) based on drug-drug-interactions. No HIV virological breakthrough occurred.

STARTVerso 4 participants were assigned to response-guided-therapy with either 120 or 240 mg of faldaprevir. In the high-dose group, participants were treated for 24 weeks (with triple therapy, or 12 weeks of triple therapy followed by 12 weeks of PEG-IFN/RBV). Early responders were randomized to stop treatment or continue with 24 weeks of PEG-IFN/RBV; participants without a protocol-defined early response (HCV RNA <25 IU/mL at week 4, and undetectable HCV RNA at week 8) were given 24 weeks of PEG-IFN/RBV.

In the low-dose group, participants were treated with 24 weeks of triple therapy; early responders were randomized to stop treatment or continue with 24 weeks of PEG-IFN/RBV, while those without an early response continued PEG-IFN for 24 additional weeks. Early response rates were high: 77 percent of treatment-naive participants and 88 percent of relapsers met criteria for shortened treatment; by week 12, HCV RNA was undetectable in 82 percent of treatment-naive participants and 91 percent of relapsers.

The most common side effects were nausea, fatigue, diarrhea, and headache. Serious adverse events (reported in <1% of participants) were fever, abdominal pain, diarrhea, rash, diarrhea, vomiting, dehydration, and gastroenteritis; anemia and neutropenia were also reported. Three deaths occurred: two were not considered related to study drug, and the third, due to drug reaction with eosinophilia and systematic systems (DRESS), is under review.[40]

Simeprevir plus PEG-IFN and RBV

TMC435-C212 is an ongoing HCV treatment trial in 106 treatment-naive or treatment-experienced people coinfected with HIV and HCV genotype 1. Prior relapsers and treatment-naive participants were assigned to response-guided therapy with 12 weeks of simeprevir plus PEG-IFN/RBV, followed by 12 or 36 weeks of PEG-IFN and RBV; partial and null responders and people with cirrhosis were assigned to 12 weeks of triple therapy, followed by 36 weeks of PEG-IFN and RBV. Of the 106 participants, 93 were receiving ART (with raltegravir-, rilpivirine-, maraviroc-, or enfuvirtide-based regimens. The median CD4 cell count was 629 cells/uL (561 in the ART arm vs. 677 in the no-ART arm). No HIV virological breakthrough occurred.

Interim results are promising: of the 88 percent (52 of 59) eligible for shortened treatment, 34 have reached posttreatment week 4 (SVR-4); 85 percent maintained undetectable HCV RNA. SVR-4 rates did not differ significantly by treatment history (84% of treatment-naive; 90% of relapsers). A subset reached posttreatment week 12; in this group, SVR-12 was 75 percent (9 of 12). Relapse has been reported only in people with HCV genotype 1a. At the time of analysis, 64 percent of null responders remained on treatment.

Safety was described as similar to that reported in HCV monoinfection, with four people discontinuing for adverse events. Common side effects were fatigue, headache, nausea, pruritus, and rash. Common laboratory abnormalities were anemia, neutropenia, elevated ALT/AST, and increased bilirubin; almost all were mild to moderate.[43]

A Novel Approach

MicroRNAs are present in human cells; they regulate gene expression. MicroRNA 122 (miR-122) is found in liver cells; it binds to hepatitis C virus, stabilizing it and stimulating viral replication.[44]

A drug targeting miR-122, called miravirsen, is being studied in HCV genotype 1 (although it is pangenotypic). Study participants were given five weekly injections of miravirsen (at doses of 3 mg, 5 mg, or 7 mg per kilogram) over 29 days, and followed for 18 weeks. Miravirsen had a dose-dependent effect: one participant in the 5 mg dosing group and four people in the 7 mg dosing group achieved undetectable HCV RNA during the study; and one person in the high-dose group maintained undetectable HCV RNA throughout 18 weeks of follow-up. No posttreatment viral resistance was observed.

Adverse events (headache, fatigue, nausea, rash, diarrhea, myalgia, flu-like symptoms, nasopharyngitis, pruritus, and injection-site reactions) were mild to moderate (with the exception of a single case of neutropenia). There were no discontinuations.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (GGT) decreased during treatment, while serum creatinine and alkaline phosphatase levels were slightly elevated.

Miravirsen has potential as a supplemental therapy: it could be administered once monthly, has a high resistance barrier, is pangenotypic, and is not expected to have significant drug-drug interactions with DAAs or other commonly used medications.[45,46] A phase II trial is evaluating 12 weeks of miravirsen in null responders with HCV genotype 1.

From Excess to Access

The buck stops—and shrinks—when it comes to HCV treatment. The extortionate pricing of first-generation HCV protease inhibitors—added to the already high cost of peginterferon and ribavirin—limits treatment access even in wealthy countries. Oversight of complex treatment algorithms, frequent monitoring requirements during

treatment, and management of nasty side effects add to the expense. A recent analysis from Mount Sinai Medical Center in New York City found that the median cost for telaprevir-based triple therapy was $98,348.[47] Although the future standard of care will be safer and more effective, require less monitoring, and be easier to administer, any savings will be eclipsed by the high cost of new drugs.

The swift and astounding progress against hepatitis C virus will have a negligible impact on public health if medicines are too costly. In low- and middle-income countries (LMICs) millions of people with hepatitis C will go without treatment if governments cannot afford drugs, or the health care systems that will administer them. For more information about movements to create and broaden access to HCV treatment in LMIC, (see Karyn Kaplan's *Low- and Middle-Income Countries Defuse Hepatitis C, the "Viral Time Bomb"* on page 191).

Where Should All the Research Go?

In the absence of public-private research networks, the race to dominate the HCV market has consequences for people with hepatitis C and their medical providers. People with the most urgent need for HCV treatment are almost always excluded from clinical trials. Enrolling healthier people in early-phase trials is sensible, but delaying trials in people with advanced liver disease until after drugs have already been approved is cruel and unacceptable.

- **Regulators, activists, patient groups, and legislators need to revisit early access programs, and create a framework that allows access to potentially lifesaving treatment for patients who are too ill or otherwise ineligible for clinical trials, while safety and efficacy data are collected.**

Activists deserve complete information about the HCV drugs they are fighting for. But the clinical definition of "hard to treat" relies on certain host and viral factors; it does not include poverty, incarceration, addiction, and mental illness—and these are rife among people with HCV. When these conditions are ignored, history demonstrates that epidemics flourish. Public-private research partnerships can integrate implementation science into drug development—by exploring and optimizing models to deliver HCV care and treatment to current and former injecting drug users and people with psychiatric disorders—without slowing down approval.

- **Governments, pharmaceutical companies, and foundations should support public-private research networks, and civil-society representatives should participate in development and oversight of these networks.**

Promising cross-company development programs have been nipped in the bud because sponsors are unwilling to split profits. This has prevented further exploration of highly effective regimens that people may want to use, despite the lack of information from larger trials.

- **Regulatory agencies need to identify metrics that will facilitate reimbursement for off-label use, keeping in mind both class-specific and within-class-specific differences in drug potency, resistance barrier, safety, and side-effect profile.**

People who are coinfected with HIV and HCV ought to be a priority population, since HIV is a known accelerant of HCV-associated liver disease, and some infrastructure for treatment delivery already exists. But trials in HIV/HCV coinfection are lagging: as of May 2013, there was only one peginterferon-free trial in coinfected people, amid dozens of trials in HCV monoinfection.

- **Sponsors should be obligated to conduct relevant DDI studies prior to phase III, to facilitate pre-approval trials in HIV/ HCV coinfection.**

The drugs are almost here. All we need is the political will to support research, develop or expand treatment infrastructure, and provide widespread access to HCV treatment.

Endnotes

1. Chen J, Florian J, Carter W, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013 Mar 5. doi: 10.1053/j.gastro.2013.02.039.
2. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. High rate of sustained virologic response with the all-oral combination of daclatasvir (NS5A Inhibitor) plus sofosbuvir (nucleotide NS5B inhibitor), with or without ribavirin, in treatment-naive patients chronically infected with HCV genotype 1, 2, or 3 (Abstract LB-2). Paper presented at: 63rd Annual Meeting of the American Association for the Study of Liver Diseases; 2012 November 9–13; Boston, MA.
3. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Sustained virologic response with daclatasvir plus sofosbuvir ± ribavirin (RBV) in chronic HCV genotype (GT) 1-infected patients who previously failed telaprevir (TVR) or boceprevir (BOC) (Abstract 1417). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.
4. Lawitz E, Ghalib R, Rodriguez-Torres M, et al. Suppression of viral load through 4 weeks post-treatment: results of a once-daily regimen of simeprevir + sofosbuvir with or without ribavirin in hepatitis C virus GT 1 null responders (Abstract 155 LB). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013 March 3–6; Atlanta, GA. Available from: http://www.retroconference.org/2013b/Abstracts/47930.htm. (Accessed 2013 April 19)
5. Presidio Pharmaceuticals (Press Release). Presidio Pharmaceuticals announces collaboration with Boehringer Ingelheim. 2013 March 12. Available from: http://www.presidiopharma.com. (Accessed 2013 March 26)
6. Merck (Press Release). Merck enters agreement with Bristol-Myers Squibb to conduct a phase II clinical trial evaluating combination of investigational oral candidates MK-5172 and daclatasvir for chronic hepatitis C. 2013 April 22. Available from: http://www.mercknewsroom.com/press-release/research-and-development-news/merck-enters-agreement-bristol-myers-squibb-conduct-phas. (Accessed 2013 May 2)
7. Idenix Pharmaceuticals (Press Release). Idenix Pharmaceuticals announces collaboration with Janssen to initiate phase II all-oral combination studies including IDX719, simeprevir (TMC435) and TMC647055 for the treatment of hepatitis C virus (HCV). 2013 January 28. Available from: http://ir.idenix.com/releasedetail.cfm?ReleaseID=735966. (Accessed 2013 May 8)
8. Janssen Pharmaceuticals (Press Release). Janssen announces collaboration with Vertex on phase 2 study to investigate an all-oral regimen of simeprevir (TMC435) and VX-135 for treatment of hepatitis C. 2012 November 1. Available from: http://www.jnj.com/connect/news/all/janssen-announces-collaboration-with-vertex-on-phase-2-study-to-investigate-an-all-oral-regimen-of-simeprevir-tmc435-and-vx-135-for-treatment-of-hepatitis-c. (Accessed 2013 May 8)
9. Vertex Pharmaceuticals (Press Release). Vertex enters agreement with Bristol-Myers Squibb for phase 2 all-oral studies of VX-135 in combination with daclatasvir for the treatment of hepatitis C. 2013 April 5. Available from: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=754494. (Accessed 2013 April 5)
10. Vertex Pharmaceuticals (Press Release). Vertex enters agreement with GlaxoSmithKline for phase 2 all-oral study of VX-135 and GSK2336805 for the treatment of hepatitis C. 2012 November 1. Available from: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=717777. (Accessed 2013 March 27)

11. Manns M, Marcellin P, Poordad F, et al. Simeprevir with peginterferon-a2a or a-2b in treatment naive HCV genotype 1 patients: QUEST-2, a randomized 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.

12. Jacobson I, Dore GJ, Foster GR, et al. Simeprevir (TMC 435) with peginterferon/ribavirin for chronic HCV genotype 1 infection in treatment-naive 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.

13. Ouwerkerk-Mahadevan S, Simion A Spittaels K, Beumont-Mauviel M. Pharmacokinetics of simeprevir (TMC435) in volunteers with moderate or severe hepatic impairment (Abstract 887). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

14. Ferenci P, Asselah T, Foster GR, et al. Faldaprevir plus pegylated interferon alfa-2a and ribavirin in chronic HCV genotype-1, treatment-naive patients: final results from STARTVerso 1, a randomized, double-blind, placebo-controlled phase III trial (Abstract 1416). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

15. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013 Jan 3;368(1):34-44. doi: 10.1056/NEJMoa1208953.

16. Osinusi A, Bon D, Herrmann E, et al. High efficacy of sofosbuvir with weight-based ribavirin for 24 weeks in difficult-to-treat patients. (Abstract157LB). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013 March 3–6; Atlanta, GA. Available from: http://www.retroconference.org/2013b/Abstracts/47966.htm. (Accessed 2013 April 12)

17. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. Lancet. 2013 Mar 14. doi: 10.1016/S0140-6736(13)60247-0.

18. Lawitz E, Mangia A, Wyles D, et al. (Fission and Neutrino) Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 Apr 23. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1214853. (Accessed 2013 May 3)

19. Gane EJ, Hyland R, Ding X, et al. ELECTRON: 100% suppression of viral load through 4 weeks' post-treatment for sofosbuvir + ledipasvir (GS-5885) + ribavirin for 12 weeks in treatment-naive and -experienced hepatitis C virus GT 1 patients (Abstract 41LB). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013 March 3–6; Atlanta, GA. Available from: http://www.retroconference.org/2013b/Abstracts/47869.htm. (Accessed 2013 April 19)

20. Gilead Sciences (Press Release). Gilead reports interim data from phase II LONESTAR study. 2013 May 2. Available from: http://www.gilead.com/news/press-releases/2013/5/gilead-reports-interim-data-from-phase-2-lonestar-study. (Accessed 2013 May 2)

21. Kowdley KV, Lawitz E, Poordad F, et al. Safety and efficacy of interferon-free regimens of ABT-450/r, ABT-267, ABT-333 +/- ribavirin in patients with chronic HCV genotype 1: results from the AVIATOR study (Abstract 3). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

22. Everson GT, Simms KD, Rodriguez-Torres M, et al. Interim analysis of an interferon (IFN)-and ribavirin-(RBV) free regimen of daclatasvir (DCV), asunaprevir (ASV) and BMS-791325 in treatment-naive, hepatitis C virus genotype 1-infected patients (Abstract 1423). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013. April 24–28; Amsterdam, the Netherlands.

23. Basaranoglu M, Basaranoglu G. Pathophysiology of insulin resistance and steatosis in patients with chronic viral hepatitis. World J Gastroenterol. 2011 Sep 28;17(36):4055–62. doi: 10.3748/wjg.v17.i36.4055.

24. Mangia A, Mottola L, Piazzolla V. Update on the treatment of patients with non-genotype 1 hepatitis C virus infection. Clin Infect Dis. 2013 May;56(9):1294–300. doi: 10.1093/cid/cis1195.

25. McPhee F, Sheaffer AK, Friborg J, et al. Preclinical profile and characterization of the hepatitis C virus NS3 protease Inhibitor Asunaprevir (BMS-650032). Antimicrob Agents Chemother. 2012 Oct;56(10):5387–96. doi: 10.1128/AAC.01186-12.

26. Moreno C, Berg T, Tanwandee T, et al. Antiviral activity of TMC435 monotherapy in patients infected with HCV genotypes 2-6: TMC435-C202, a phase IIa, open-label study. J Hepatol. 2012 Jun;56(6):1247–53. doi: 10.1016/j.jhep.2011.12.033.

27. Silva MO, Treitel M, Graham DJ, et al. Antiviral activity of boceprevir monotherapy in treatment-naive subjects with chronic hepatitis C genotype 2/3. J Hepatol. 2013 Feb 27. doi: 10.1016/j.jhep.2013.02.018.

28. White PW, Llinàs-Brunet M, Amad M, et al. Preclinical characterization of BI 201335, a C-terminal carboxylic acid inhibitor of the hepatitis C virus NS3-NS4A protease. Antimicrob Agents Chemother. 2010 Nov;54(11):4611–8. doi: 10.1128/AAC.00787-10.

29. Seiwert SD, Andrews SW, Jiang Y, et al. Preclinical characteristics of the hepatitis C virus NS3/4A protease inhibitor ITMN-191 (R7227). Antimicrob Agents Chemother. 2008 Dec;52(12):4432–41. doi: 10.1128/AAC.00699-08.

30. Cheng G, Peng B, Corsa A, et al. Antiviral activity and resistance profile of the novel HCV NS5A inhibitor GS-5885 (Abstract 1172). Paper presented at: 47th Annual Meeting of the European Association for the Study of the Liver; 2012 April 18–22; Barcelona, Spain.

31. Hernandez D, Zhou N, Ueland J, Monikowski A, McPhee F. Natural prevalence of NS5A polymorphisms in subjects infected with hepatitis C virus genotype 3 and their effects on the antiviral activity of NS5A inhibitors. J Clin Virol. 2013 May;57(1):13–8. doi: 10.1016/j.jcv.2012.12.020.

32. Dore GJ, Lawitz E, Hézode C, et al. Daclatasvir combined with peginterferon alfa 2a and ribavirin for 12 or 16 weeks in patients with hepatitis C virus genotype 2 or 3 infection: COMMAND GT 2/3 study (Abstract 1418). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

33. Gane EJ, Rodriguez-Torres M, Nelson DE, et al.. Sustained virologic response following RG7128 1500mg BID/PEG-IFN/RBV for 28 days in HCV genotype 2/3 prior non-responders (Abstract 37). Paper presented at: 45th Annual Meeting of the European Association for the Study of the Liver; 2010 April 14–18; Vienna, Austria. http://www.kenes.com/easl2010/Orals/143.htm. (Accessed 2013 May 22)

34. Lam AM, Espiritu C, Bansal S, et al. Genotype and subtype profiling of PSI-7977 as a nucleotide inhibitor of hepatitis C virus. Antimicrob Agents Chemother. 2012 Jun;56(6):3359–68. doi: 10.1128/AAC.00054-12.

35. Soriano V, Gane EJ, Angus P, et al. Efficacy and safety of the interferon-free combination of faldaprevir (BI 201335) + BI 207127 ± ribavirin in treatment-naive patients with HCV GT-1 and compensated liver cirrhosis: results from the SOUND-C2 study A (Abstract 84). Paper presented at: 63rd Annual Meeting of the American Association for the Study of Liver Diseases; 2012 November 9–13; Boston, MA.

36. Rutter K, Ferlitsch A, Maieron A, et al. Safety of triple therapy with telaprevir or boceprevir in hepatitis C patients with advanced liver disease-predictive factors for sepsis (Abstract 65). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.

37. Hernando V, Perez-Cachafeiro S, Lewden C, et al; CoRIS. All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. J Hepatol. 2012 Oct;57(4):743–51. doi: 10.1016/j.jhep.2012.06.010.

38. van der Helm J, Geskus R, Sabin C, et al; CASCADE collaboration in EuroCoord. Effect of HCV infection on cause-specific mortality after HIV seroconversion, before and after 1997. Gastroenterology. 2013 Apr;144(4):751–760.e2. doi: 10.1053/j.gastro.2012.12.026.

39. Ioannou GN, Bryson CL, et al. The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. Hepatology. 2013 Jan;57(1):249–57. doi: 10.1002/hep.25800.

40. Dieterich D, Soriano V, Nelson M, et al. STARTVerso 4: high rates of early virologic response in hepatitis C virus genotype 1/HIV co-infected patients treated with faldaprevir + pegylated interferon and ribavirin (Abstract 40LB). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013 March 3–6; Atlanta, GA. Available from: http://www.retroconference.org/2013b/Abstracts/47927.htm. (Acccessed 2013 May 3)

41. Martel-Laferriere V, Brinkley S, Bichoupan K, et al. On-treatment responses to telaprevir-based hepatitis C treatment are similar in HIV/hepatitis C virus co-infected and hepatitis C virus mono-infected patients (Abstract 679). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013 March 3–6; Atlanta, GA. http://www.retroconference.org/2013b/PDFs/679.pdf. (Accessed 2013 April 5)

42. Sulkowski MS Sherman KE, Soriano V, et al. Telaprevir in combination with peginterferon alfa-2a/ribavirin in HCV/HIV co-infected patients: SVR24 final study results (Abstract 54). Paper presented at: 63rd Annual Meeting of the American Association for the Study of Liver Diseases; 2012 November 9–13; Boston, MA.

43. Dieterich D, Rockstroh J, Orkin C, et al. Simeprevir with pegylated interferon/ribavirin in patients co-infected with chronic hepatitis C virus and HIV-1: week-24 interim analysis of the TMC435-C212 study (Abstract 154LB). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013 March 3–6; Atlanta, GA. Available from: http://www.retroconference.org/2013b/Abstracts/47929.htm. (Accessed 2013 April 19)

44. Mortimer SA, Doudna JA. Unconventional miR-122 binding stabilizes the HCV genome by forming a trimolecular RNA. Nucleic Acids Res. 2013 Apr 1;41(7):4230–40. doi: 10.1093/nar/gkt075.

45. Janssen HL, Reesink HW, Lawitz EJ, et al. Treatment of HCV infection by targeting microRNA. N Engl J Med. 2013 May 2;368(18):1685–94. doi: 10.1056/NEJMoa120902.

46. Li YP, Gottwein JM, Scheel TK, Jensen TB, Bukh J. MicroRNA-122 antagonism against hepatitis C virus genotypes 1-6 and reduced efficacy by host RNA insertion or mutations in the HCV 5′ UTR. Proc Natl Acad Sci U S A. 2011 Mar 22;108(12):4991–6. doi: 10.1073/pnas.1016606108.

47. Bichoupan K, Martel-Laferriere V, Ng M. et al. Real world costs of telaprevir-based triple therapy, including costs of managing adverse events, at the Mount Sinai Medical Center, NY: $147,000 per EOT (Abstract 795). Paper presented at: 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24–28; Amsterdam, the Netherlands.