Infectious Diseases

Science is yielding important new options against hepatitis C. All-oral therapies that can cure the disease in three months, without injected interferon, are on the horizon. But there are potential headwinds. **Noah Pines** sorts out the frontrunners in hep. C and elsewhere in the pipeline

For those awaiting changes in the treatment of hepatitis C, it's almost time to toss the confetti. The field is on the verge of one of the most profound upgrades in any therapeutic category, promising real progress in efficacy, tolerability and convenience. Barring any safety bombshells, a prolific pipeline of direct-acting anti-viral agents (DAAs) is due to start issuing forth options that, when combined, will permit all-oral, interferon-free treatment.

By making future HCV treatment shorter, safer, easier and more effective, says Jonathan Fenkel, MD, director of the hep. C center at Thomas Jefferson University, these protocols "will open the door to many more patients who have declined or deferred treatment."

That could mean billions in sales. Analysts say new therapies could help grow the pie for the virus to $20 billion annually by 2020. The infectious diseases market, as a whole, rose from $33.6 billion in 2011, to $35.2 billion in 2012, according to data compiled by IMS Health on sales of hep. C and HIV drugs, as well as antibiotics and vaccines.

Clinicians and analysts agree that the first and likely go-to therapy will eventually be Gilead Sciences' sofosbuvir (GS-7977). Gilead has applied for approval of sofosbuvir and ribavirin as an all-oral therapy for patients with genotypes 2 and 3—the minority of patients with hep. C in the US (about 75% of patients are genotype 1).

Gilead's agent is the "holy grail of HCV treatment," analyst Julie Hoggatt tells *MM&M*. The first hep. C drug to cut treatment duration to 12 weeks, vs. 24 weeks with the available DAAs (Vertex's Incivek or Merck's Victrelis), it boosts efficacy from a 70% cure rate to over 80%. Phase II data from Gilead suggest a further 33% reduction in treatment duration—from 12 weeks down to eight—in patients taking a combination of sofosbuvir and Gilead's ledipasvir, aka GS-5885.

The nucleotide analogue polymerase inhibitor (or "nuc") has broad-spectrum genomic activity (meaning that it covers multiple hep. C genotypes), a barrier to the development of viral resistance, has once-daily dosing, and can be co-formulated with other agents.

PHOTO: THINKSTOCK

Other players include AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Merck, Vertex and smaller biotechs. Some could find a niche among the difficult-to-treat population. But, says Hoggatt, a principal with Symphony Health Solutions' *in*Thought Research, "We are forecasting Gilead to be the clear majority player, with sofosbuvir capturing 75% peak market share." She predicts approval as early as mid-December for use in genotypes 2 and 3. By 2015, sofosbuvir's label is likely to be expanded as part of an all-oral regimen for the more common genotype 1, when combined with ledipasvir.

In the meantime, *in*Thought expects some off-label use of sofos-

TOP 50 INFECTIOUS DISEASES PRODUCTS, 2012

Category leaders, ranked by US sales, and their media spend

Rank	Product	Manufacturer	US sales $ (millions)*	Vs. prior 12 mos.	TRx (000s)	Vs. prior 12 mos.	US DTC media $ (000s)	Vs. prior 12 mos.	US journal media $ (000s)	Vs. prior 12 mos.
1	**Atripla**	BMS/Gilead	$2,898.2	11.0%	1,351.0	2.0%	$799.0	>100.0%	$1,004.4	-11.0%
2	**Truvada**	Gilead	$2,304.5	15.0%	1,654.0	5.0%	$13.8	100.0%	$59.2	N/A
3	**Avonex**	Biogen Idec	$1,703.3	1.0%	356.0	-15.0%	$128.1	1.0%	$921.3	48.0%
4	**Incivek**	Vertex	$1,380.5	59.0%	N/A	N/A	$7,805.3	>100.0%	$1,605.6	>100.0%
5	**Rebif**	EMD Serono/Pfizer	$1,245.8	11.0%	N/A	N/A	$2.0	13.0%	$100.9	-66.0%
6	**Reyataz**	BMS	$986.9	3.0%	793.0	-2.0%	$565.7	23.0%	$824.0	-34.0%
7	**Isentress**	Merck	$953.4	21.0%	785.0	15.0%	$277.8	>100.0%	$233.1	N/A
8	**Prezista**	Johnson & Johnson	$842.5	32.0%	665.0	20.0%	$0.0	-100.0%	$735.2	-3.0%
9	**Betaseron**	Bayer HealthCare	$820.3	5.0%	N/A	N/A	$0.0	N/A	$58.8	-69.0%
10	**Varivax**	Merck	$814.4	1.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
11	**Prevnar 13**	Pfizer	$776.4	-4.0%	N/A	N/A	$40.8	-100.0%	$599.0	-30.0%
12	**Zyvox**	Pfizer	$721.8	-1.0%	N/A	N/A	$0.6	-50.0%	$828.3	-27.0%
13	**Zostavax**	Merck	$653.1	76.0%	2,509.0	105.0%	$46,037.1	>100.0%	$10.8	N/A
14	**Cubicin**	Cubist	$615.3	4.0%	N/A	N/A	$0.0	N/A	$655.2	-10.0%
15	**Solodyn**	Medicis	$603.2	-23.0%	910.0	-30.0%	$0.0	-100.0%	$74.5	4.0%
16	**Gardasil**	Merck	$585.6	42.0%	N/A	N/A	$43,659.7	-1.0%	$0.0	N/A
17	**Pegasys Conven Pac**	Roche	$584.1	9.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
18	**Viread**	Gilead	$543.0	15.0%	600.0	4.0%	$0.0	N/A	$336.3	-48.0%
19	**Epzicom**	ViiV Healthcare	$521.9	8.0%	454.0	3.0%	$0.0	-100.0%	$0.0	N/A
20	**Norvir**	Abbott	$509.7	3.0%	1,467.0	5.0%	$0.0	N/A	$0.0	N/A
21	**Valacyclovir HCl**	Generic	$471.8	-35.0%	10,745.0	8.0%	$0.0	N/A	$0.0	N/A
22	**Penumovax 23**	Merck	$455.9	21.0%	693.0	34.0%	$242.2	100.0%	$1,122.5	N/A
23	**Vancomycin HCl**	Generic	$406.2	>100.0%	632.0	33.0%	$0.0	N/A	$0.0	N/A
24	**Adacel**	Sanofi Pasteur	$397.9	-9.0%	N/A	N/A	$0.0	-100.0%	$0.0	-100.0%
25	**Valcyte**	Genentech	$396.5	19.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
26	**Azithromycin**	Generic	$388.9	-17.0%	54,057.0	-2.0%	$0.0	N/A	$0.0	N/A
27	**Zosyn**	Pfizer	$380.7	-16.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
28	**Tamiful**	Roche	$353.3	35.0%	3,431.0	15.0%	$31,911.9	>100.0%	$190.1	-39.0%
29	**Amox tr/pot clavul**	Generic	$352.7	-19.0%	22,325.0	0.0%	$0.0	N/A	$0.0	N/A
30	**Complera**	Gilead	$349.0	>100.0%	N/A	N/A	$673.4	>100.0%	$1,559.1	>100.0%
31	**Kaletra**	Gilead	$333.0	-12.0%	379.0	-15.0%	$0.0	-100.0%	$346.7	-68.0%
32	**Tobi**	Novartis	$332.2	15.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
33	**Menactra**	Sanofi Pasteur	$302.8	-8.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
34	**Victrelis**	Merck	$273.4	>100.0%	N/A	N/A	$0.0	N/A	$640.6	-11.0%
35	**Baraclude**	BMS	$265.8	27.0%	N/A	N/A	$0.0	N/A	$11.6	-50.0%
36	**Cefdinir**	Generic	$253.8	15.0%	9,342.0	-2.0%	$0.0	N/A	$0.0	-100.0%
37	**Avonex Pen**	Biogen Idec	$248.5	N/A	356.0	-15.0%	$0.0	N/A	$0.0	N/A
38	**Avelox**	Bayer HealthCare	$240.6	-31.0%	1,561.0	-38.0%	$0.0	N/A	$0.0	N/A
39	**Fluvirin**	Novartis	$240.3	20.0%	2,949.0	24.0%	$0.0	N/A	$0.0	N/A
40	**Invanz**	Merck	$235.7	11.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
41	**Doryx**	Warner Chilcott	$226.5	-23.0%	543.0	-14.0%	$0.0	N/A	$0.0	N/A
42	**M-M-R-II**	Merck	$218.9	11.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
43	**Intelence**	Johnson & Johnson	$209.7	14.0%	N/A	N/A	$0.0	-100.0%	$0.0	N/A
44	**Rotateq**	Merck	$207.0	-1.0%	N/A	N/A	$0.0	-100.0%	$238.6	-6.0%
45	**Boostrix**	GlaxoSmithKline	$197.7	37.0%	352.0	>100.0%	$0.3	>100.0%	$593.1	69.0%
46	**Pentacel**	Sanofi Pasteur	$191.0	-18.0%	N/A	N/A	$0.0	-98.0%	$119.2	-75.0%
47	**Amoxicillin**	Generic	$185.2	-12.0%	52,024.0	-3.0	$0.0	N/A	$7.0	N/A
48	**Sustiva**	BMS	$180.3	-7.0%	N/A	N/A	$1.6	>100.0%	$176.0	-23.0%
49	**Pegasys ProClick**	Roche	$174.3	>100.0%	N/A	N/A	$0.0	N/A	$0.0	N/A
50	**Engerix-B**	GlaxoSmithKline	$167.5	-7.0%	N/A	N/A	$0.0	N/A	$0.0	N/A

Sources: Sales/TRx, IMS Health; DTC media spend, Nielsen; journals, Kantar Media.
Note: List includes products FDA indicates as approved for treating AIDS, hepatitis B/C and bacterial infections, as well as vaccines and other antivirals.

CLINICAL CORNER

The days of interferon are numbered. So, what are the next important milestones in the evolution of hepatitis C drug development? The two next big signposts, sources say, are the removal of ribavirin from treatment protocols as well as the further truncating of HCV regimens to as short as eight weeks, down from today's 24-48.

Ribavirin is a double-edged sword. It has been shown to reduce the rate of relapse and it's cheap. But it's a weak anti-viral whose mechanism of action against HCV is not well understood, and it's dosed twice daily. RBV, as it's known, also brings such side effects as anemia, so physicians can't dose it in patients with kidney impairment, and teratogenicity (a contraindication in pregnant women).

Wayne Dankner

The latter "complicates recruiting women of child-bearing age into clinical trials—a substantial number of HCV patients!" says Wayne Dankner, MD, global therapeutic area lead for infectious diseases and pediatrics with the CRO Parexel. It also affects male subjects as they must "practice adequate birth control with their female partners," he adds.

Multiple strains of evidence from the clinical literature suggest that it may be possible to show ribavirin the door. Manufacturers like Gilead, AbbVie and Bristol-Myers Squibb are trying to identify other direct-acting anti-virals that can replace RBV in the regimen or to find agents that are sufficiently robust to obviate the need for it altogether.

The other opportunity on the horizon is to reduce the duration of therapy—an opportunity highlighted by the announcement of Gilead's Phase II Lonestar data in early May. Lonestar demonstrated a 95-100% cure rate after eight weeks of therapy with a fixed dose combination of Gilead's nuc sofosbuvir plus the NS5a ledipasvir (GS-5885).

"While most of these regimens are 12 weeks in duration, there is a continual focus on whether we can shorten to eight weeks. That would improve acceptance and lessen exposure to drugs," says Dankner.

Another important future development is providing effective therapy to patients with more advanced liver disease, such as cirrhosis, and those with multiple co-morbidities, including HCV/HIV co-infection. Such patients have historically been much more difficult to treat.

"Enrollment of a population representative of the disease being treated is critically important," says Peter Piliero, MD, Boehringer Ingelheim VP, clinical development and medical affairs. Other typical patient characteristics, Piliero adds, include those with both HCV genotype 1 subtypes (1a and 1b) and the various IL28b polymorphisms.

But scientists looking for new HCV treatments are not starting from scratch. Most of the companies in the field have cut their teeth developing antiretroviral agents for HIV. "We'll have a second generation of agents coming right on the heels of the first generation," says UCSD School of Medicine's Bob Gish, MD, chief of clinical hepatology and professor of clinical medicine. "The warp speed we're seeing is because of that historical experience in other viral illnesses."

buvir plus ribavirin without interferon in treatment-naïve genotype 1 patients, the analyst wrote in an April research note in which she modeled peak worldwide sales of $4.3 billion for sofosbuvir. This is a conservative forecast, below street consensus which is over $7 billion.

"Shortening treatment and lowering the pill burden will have a huge effect on compliance, efficacy, and acceptance," says Jefferson's Fenkel. Not to mention safety: IMS analyst Steve Gubernick notes, "You don't have to worry about paying for side effects anymore."

This is a wholesale transformation from today's standard of care, which incorporates pegylated interferon (PEG-IFN), ribavirin and a protease inhibitor (Incivek or Victrelis). Many of today's HCV treaters are holding patients back until the new wave of oral medication hits.

According to Hoggatt and others, the next most-dominant company in the HCV market after Gilead will likely be AbbVie, whose multi-drug oral regimen has high efficacy among null responders. It scored FDA's "breakthrough" status, as did BMS hep. C drug daclatasvir.

In testing, daclatasvir with asunaprevir and BMS-791325, produced a high cure rate in prior treatment failures. And BI presented data on NS3/4a protease inhibitor faldaprevir which, in conjunction with pegylated interferon and RBV, had a 79-80% rate of cure in a group that had a high proportion of tough-to-treat cirrhotic patients.

Hep. C is, for most patients, not fast-moving, so they can wait for new options. In a research note, ISI Group analyst Mark Schoenebaum, MD, estimated that around 350,000 US patients are under the care of a hep. C specialist and can be easily accessed and activated once new treatments arrive. The challenge is getting patients diagnosed and into the medical system; and, once they are, managing the potential flood of treatment-eligible patients. There are about three million infected patients in the US, four million in Western Europe, about a million in Japan and seven million in Eastern Europe.

Another caveat: Who'll pay for the new regimens, which could cost $100,000 or more for a three-month course. While today's regimens cost from $65,000-$80,000, according to ISI's Schoenebaum, "I [w]ould be very surprised if [sofosbuvir] were priced significantly less than $80k, and wouldn't be shocked to see $100k." *in*Thought's Hoggatt models a wholesale cost closer to $54,000 for a 12-week course.

What is dictated by the payers will be important. "If we have equal efficacy and side-effect profiles for all of the regimens, the payers may have preferences," says Paul Pockros, MD, division head of gastroenterology and hepatology at the Scripps Clinic in San Diego. Of course, all of this new drug excitement is unfolding against the backdrop of ObamaCare, rolling out in 2014. That means more people covered, but leaves guesswork as to the span of pharmaceutical coverage.

While a revolution is under way in hep. C, in HIV/AIDS it's more of an evolution. With the approval of Gilead's quad-pill Stribild, there are three one-pill, once-a-day, single-tablet regimens available, all with high efficacy and favorable tolerability. Attention is focused mostly on the safest, most convenient way to treat patients chronically for life.

"Our focus is still on the safest regimens that give patients a healthy lifespan without cumulative toxicities," says Cal Cohen, MD, a leader in HIV research and an instructor at Harvard University. Cohen spotlights two investigational anti-retroviral medications in the pipeline. Gilead's tenofovir alafenamide fumarate (TAF; GS-7340) has so far shown greater antiviral activity with potentially fewer concerns about kidney function or bone mineral density. The other investigational agent Cohen's eying is ViiV's second-generation integrase inhibitor dolutegravir, which has demonstrated sustained efficacy and once-daily dosing, without the need for a pharmacokinetic booster. ■