

HCV Pipeline: DAAs and Diagnostics in the Pangenotypic Era

By Annette Gaudino

INTRODUCTION

The continued development of direct-acting antivirals (DAAs) against hepatitis C virus (HCV) has brought both multigenotypic and pangenotypic regimens to market, with more on the horizon. These simpler-to-prescribe regimens potentially eliminate the need for genotype testing, have shown improved efficacy in previously difficult-to-treat patients, and hold the promise of massive scale up of treatment in primary care settings with nonspecialist providers, such as general internists and non-physicians, including nurse practitioners and physician assistants, as well as community pharmacists prescribing these therapies. Progress towards reliable, streamlined diagnostics that provide rapid confirmatory ribonucleic acid (RNA) testing has also continued, with manufacturers pursuing the goal of one-step point-of-care testing suitable for resource-limited settings. To effectively address the rising incidence of HCV among those who actively inject drugs, punitive approaches to drug use must be abandoned in favor of a public health approach, with people who use drugs at the center of the response.

Unless and until we can rapidly identify and treat chronically infected individuals, concrete progress towards the World Health Organization (WHO) targets on the elimination of HCV as a public health threat by 2030 will remain an elusive goal.¹ Despite possessing highly effective short-course curative treatments that are the envy of those combatting HIV and TB, without unprecedented investment in implementation of strategic public health actions against HCV, we stand to miss a historic opportunity to wipe this deadly infectious disease from the face of the earth.

Global commitments are needed to end the HCV epidemic:

- National action plans with secure, multi-year funding for HCV treatment for everyone without restrictions, including treating reinfections;
- Sustainable global funding for generics, including multigenotypic and pangenotypic DAAs, and diagnostics in low- and middle-income countries;
- R&D for more options in point-of-care RNA assays to fill critical gaps in screening programs and put more patients on treatment;
- R&D for comprehensive diagnostic technologies that ensure rapid test results in a single visit, inform treatment regime choice, and confirm curative rates in patients;
- Research to develop a new class of DAAs to cure in four weeks;
- Continued funding for research towards a HCV vaccine that shows efficacy in people at risk for HCV infection because they inject drugs; the ability to elicit immune response in people living with HIV who are not at high risk for HCV infection; and safety in combination with HIV vaccine administration in healthy volunteers;
- R&D for dosage and effective treatment regimens for infants and children (aged 3-12 years) and weighing less than 35 kilograms (77 pounds);
- Post-treatment studies on the efficacy and long-term health effects for sofosbuvir and sofosbuvir/ledipasvir in adolescents (aged 12-17 years);

- Expanded risk based screening beyond the birth cohort (1945-1965 in the U.S.; different ranges outside the U.S.)
- Decriminalization of drug use and centering the needs of those most at risk for infection.

Beyond blockbuster prices: adding tools to the toolkit

The arrival of highly effective, interferon-free, single daily dose DAAs in 2014 led to remarkably increased public awareness of HCV, but hasn't led to a comprehensive response to the epidemic. The eye-popping price of Gilead's essential compound sofosbuvir (Sovaldi) generated countless headlines and outrage as the latest example of corporate greed in the pharmaceutical industry. However, focus on the high price of HCV cures has dominated the public response to the epidemic, only slowly and haltingly generating movement on the public health challenge posed by HCV infection. Although calls to address the high price of pharmaceutical drugs have frequently used HCV cures as the exemplars of everything wrong with the status quo, the movement for drug-pricing reform has, overall, rarely engaged directly in the struggle for HCV treatment access. A broad coalition bringing together activists for patent law and drug development reform, drug user health and harm reduction, and those living with HCV could be a powerful force to demand action.

As advocates fight to be heard, recent approvals of multigenotypic and pangenotypic treatments continue to add tools to our anti-HCV toolkit. New and soon-to-be available options from multiple manufacturers not only benefit patients, especially those with advanced disease, co-morbidities, and difficult-to-treat genotype 3, but also offer payers needed flexibility when choosing regimens for their formularies. Drugs in the development pipeline, most notably AbbVie's pangenotypic combo glecaprevir/pibrentasvir (Maviret), will go head to head with Gilead's sofosbuvir/velpatasvir (Epclusa).

In high-income countries, Merck's Zepatier (grazoprevir/elbasvir) and AbbVie's Viekira Pak have been used as alternative, more-affordable regimes in patients with genotype 1 and 4. Viekira Pak is offered as a multi-pill twice daily regimen, and is not approved for patients with genotype 4 and cirrhosis. Zepatier requires pre-treatment NS5A-resistance testing in patients with genotype 1a. A new once daily formulation of AbbVie's four-drug combination, Viekira XR, was approved in July 2016, and appears to be a more attractive option for patients and providers. Gilead's drugs are not currently available through state AIDS Drug Assistance Programs (ADAP) for HIV/HCV co-infected patients in the U.S., potentially allowing AbbVie to leverage their position in ADAP formularies for their new pangenotypic combo G/P when it hits the U.S. market.

Pending drugs in the pipeline: the dawn of the pangenotypic era

AbbVie, Gilead, Merck, and Janssen have presented data at international congresses on efficacy across the six major genotypes; in difficult-to-treat populations, including patients with genotype 3 and cirrhosis; and patients with advanced kidney disease. Gilead also recently received approval for previously untreated adolescents, and presented data on ongoing clinical trials in young children. It would not be hyperbole to state that science has solved chronic HCV infection for all but individuals with decompensated cirrhosis—yet another powerful argument for early treatment. It must be noted that, as historically has been the case, all clinical trial data is based on majority male patient populations, with few people of color, particularly African Americans, taking part in clinical trials.

Table 1 (below) summarizes the latest multigenotypic and pangenotypic DAAs in the pipeline.

Table 1. Multigenotypic and Pangenotypic Treatments

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENOTYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
Glecaprevir + pibrentasvir (G/P) (300 mg/120 mg)	NDA submitted Dec 2016	AbbVie	YES	EXPEDITION-1 ^{2,3,4}	Single arm, open-label study; N=146 patients with GT1, 2, 4, 5, or 6 and compensated cirrhosis.	12 weeks	NO	NO	99% SVR; one GT1a relapse. No serious treatment-related AEs.
				EXPEDITION-2 ⁵	Open-label study comparing 8 (without cirrhosis)-and 12 weeks (with cirrhosis) G/P. N=153 HIV/HCV coinfecting patients, GT1-6 (N=16 with cirrhosis); treatment naïve or not cured with prior treatment.	8 or 12 weeks	N=153	NO	98% SVR without cirrhosis, 93% SVR with cirrhosis. No serious treatment-related AEs
				EXPEDITION-4 ⁶	Single-arm, open-label evaluation of 12 weeks G/P in patients with chronic disease (CKD); N=104 with GT1-6 and stage 4 or 5 CKD.	12 weeks	N=0	NO	98% (102/104) SVR12; , no serious treatment related AE or treatment discontinuations reported, grade 3 or higher lab abnormalities were rare
				ENDURANCE-1 ^{7,8,9}	Randomized comparisons of 8 and 12 weeks G/P. N=703 patients with GT1 and without cirrhosis; treatment naïve or not cured with prior treatment.	8 or 12 weeks	N=33	NO	95% SVRs in 12- and 8-week groups; no serious treatment-related AEs.
				ENDURANCE-3 ¹⁰	Randomized comparison of 12 weeks G/P vs. sofosbuvir/daclatasvir (SOF/DCV), with additional 8-week G/P non-inferiority comparison with 12-week G/P. N=505 treatment-naïve patients with GT3 and without cirrhosis.	8 or 12 weeks	NO	NO	Non-inferior to SOF/DCV; 95% SVRs in 12- and 8-week G/P groups; no serious treatment-related AEs

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENOTYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
				MAGELLAN-1, Part 1 ^{11,12}	Randomized comparison of 12 weeks G/P 200/80 mg (Group A; discontinued), G/P 200/120 mg plus 800 mg ribavirin (Group B), or 300/120 mg without ribavirin (Group C). N=50 GT1 patients with history of failure with NS3/4A \geq 1 NS3/4A PI or NS5A inhibitor	12 weeks	NO	Yes	SVRs of 100% in Group A, 95% in Group B, and 86% in Group C; no improvement associated with addition of ribavirin. Virologic failure in 1 patient each in Groups B and C.
				MAGELLAN-1, Part 2 ¹³	Randomized comparison of 12 and 16 weeks G/P; N=91 with GT1, 4, 5, or 6 with history of failure with \geq 1 NS3/4A PI or NS5A inhibitor (N=27 with compensated cirrhosis)	12 or 16 weeks	NO	No	Overall SVR: 89% (12 weeks) and 91% (16 weeks); 79–81% in pts. with PI + NS5A experience; 88–94% with NS5A experience only; 100% with PI experience only
sofosbuvir/ velpatasvir/ voxilaprevir (400 mg/100 mg/100 mg)	NDA submitted Dec 2016	Gilead	YES	POLARIS-1 ¹⁴ , -4 ¹⁵	Phase III multicenter randomized double-blind, placebo-controlled study in GT1-6 TE patients with/without previous NS5A inhibitor exposure, N=445	12 weeks	NO	NO	97% (241/248) SVR12 TE with NS5A inhibitor 99% (168/169) SVR12 TE without NS5A inhibitor; positioned as salvage treatment; mild GI upset reported with voxilaprevir
				POLARIS-2 ¹⁶	Phase III multicenter randomized, open label, active comparator trial, GT1-6 TN patients +/- cirrhosis, 8 weeks sof/vel/vox in vs 12 weeks sof/vel, stratified by GT, cirrhosis and TE, N=941	8 weeks	NO	NO	95% (476/501) SVR12 with 8 weeks sof/vel/vox 98% (432/440) SVR12 with 12 weeks sof/vel

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENOTYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
				POLARIS-3 ¹⁷	Phase III multicenter randomized open label active comparator trial, GT3 +/- cirrhosis, 8 weeks sof/vel/vox vs 12 weeks sof/vel, stratified by TE, N=219	8 weeks	NO	NO	96% (106/110) SVR12 with 8 weeks sof/vel/vox 2 relapse, 1 withdrawal of consent, 1 non treatment related death 96% (105/109) SVR12 with 12 weeks sof/vel 1 treatment failure, 1 relapse, 1 discontinued due to AE, 1 lost to follow up
uprifosbuvir/grazoprevir/ruzasvir (225 mg/50 mg/30 mg)	Phase II/III	Merck (MK3)	GT1, 2, 3	C-SURGE ¹⁸	Multicenter open label randomized trial of GT1 patients who previously failed LDV/SOF or EBR/GRZ, stratified by GT1a/b and cirrhosis, N=94	16/24 weeks	NO	YES with 16 weeks	GT1 TE 16 weeks + RBV 98% (43/44) SVR8 24 weeks 100% (30/30) SVR8; Neither cirrhosis, RBV, nor baseline NS3 or NS5A resistance affected SVRs.
				C-CREST B & C ¹⁹	Multicenter open label randomized trial, N=675; participants treatment-naïve to DAAs; GT3 pegIFN/RBV treatment-experienced patients included.	8/12/16 weeks	NO	YES in all arms	GT1 8 weeks 94% (83/88) SVR24, 12 weeks 94% (83/88) SVR24 GT2 8 weeks 86% (54/63) SVR24, 12 weeks 97% (60/62) SVR24, 16 weeks 100% (26/26) SVR24 GT3 8 weeks 93% (96/103) SVR24, 12 weeks 96% (153/159) SVR24, 16 weeks 96% (72/75) SVR24 GT4 8 weeks 100% (7/7) SVR12 GT6 12 weeks 100% (4/4) SVR12 1 discontinued due to AE, 1 reinfection GT1 8 weeks

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENOTYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
AL-335 (NS5B nuc)/odasvir (NS5A) +/- simeprevir (PI) (800 mg/50 mg/75 mg)	Phase II	Janssen (JNJ-4178)	GT1, 3	OMEGA-1 NCT02765490 ²⁰	International Phase IIb multicenter, randomized, open-label study of GT1, 2, 4, 5 and 6 without cirrhosis, fully enrolled	6/8 weeks	NO	NO	GT1 TN* 6 or 8 weeks 100% SVR, GT3 TN 12 weeks 77% SVR
sofosbuvir/velpatasvir (400 mg/100 mg)	Approved	Gilead (Epclusa)	YES	ASTRAL-1 ²¹ , -2 ²² , -3 ^{23,24}	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	12 weeks	YES	With decompensated cirrhosis	>90% SVR except GT3 TE with decompensated cirrhosis* 89% SVR
sofosbuvir/ledipasvir (400 mg/90 mg)	Approved	Gilead (Harvoni)	GT1, 4, 5 & 6			12 weeks, consider 8 weeks with low viral load	YES	GT1, GT4 TE with decompensated cirrhosis	Approved for use post-transplant with RBV; >90% SVR except GT1 with decompensated cirrhosis*
dasabuvir/paritaprevir/ritonavir/ombitasvir (600 mg/150 mg/100 mg/25 mg)	Approved new QD formulation	AbbVie (Viekira XR)	GT1, GT4 w/out cirrhosis			12 weeks, 24 weeks in GT1 with cirrhosis	GT1	GT1a, GT4	>90% SVR; Can cause resistance to HIV ARVs
grazoprevir/elbasvir (100 mg/50 mg)	Approved	Merck (Zepatier)	GT1, 4			12 weeks, 16 weeks TE	YES	With NS5A resistance or GT4 TE	>90% SVR except GT1 TE with protease inhibitor resistance
sofosbuvir/daclatasvir (400 mg/60 mg)	Approved components	Gilead (Sovaldi), BMS (Daklinza)	GT1, 3	REDEMPTION trials ²⁵ ; ALLY-1, 2, 3, 3+ ^{26,27}	Phase 3 open label, non randomized, parallel assignment study; few GT4, GT5, or GT6 patients enrolled.	12 weeks	YES	GT1 decompensated cirrhosis or post transplant	GT1 96% SVR, GT2 100% SVR, GT3 87% SVR, GT4 91% SVR, GT5/6 100%
sofosbuvir/ledipasvir (400 mg/90 mg) for >12 yrs, >35kg	Approved supplemental application	Gilead (Harvoni)	GT1, 4, 5, 6	Gilead Long Term Follow-up Registry ²⁸	Observational prospective cohort study (5 years)	12 weeks	NO	NO	approved on previous data

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sofosbuvir (400 mg) + ribavirin for >12 yrs, >35kg	Approved supplemental application	Gilead (Sovaldi)	GT2, 3	Gilead Long Term Follow-up Registry ²⁹	Observational prospective cohort study (5 years)	12 weeks, 24 weeks	NO	YES	GT2 100% SVR, GT3 97% SVR, No serious treatment related AE, most common AE were fatigue, headache, nausea
sofosbuvir/ledipasvir (200 mg/45 mg) +/- ribavirin for ages 6-11 yrs	Phase III	Gilead (Harvoni)	GT1, 3, 4	Gilead Long Term Follow-up Registry ³⁰	Observational prospective cohort study (5 years) for ages 6-11; international multi-site open label trial with children aged 3-6 ongoing	12 weeks, 24 weeks	NO	With cirrhosis	12 weeks 99% SVR, 24 weeks 100% SVR, 24 weeks + RBV 100% SVR All patients received 12 weeks except GT3 (n=2) and GT1 TE patient with cirrhosis (n=1); No treatment related AE or treatment discontinuations reported

AE: adverse events.

NDA: new drug application.

QD: once daily.

TE: treatment experienced.

TN: treatment naive.

*decompensated cirrhosis defined as Child-Pugh B/C

Treatment duration: how short can we go?

Shortening treatment duration has been of interest to patients and providers since the development of interferon-based treatments. Cost is usually understood as the unstated reason for seeking to go shorter. For example, cost savings may have motivated recent real-life studies of eight-week courses of ledipasvir/sofosbuvir at the Veterans Administration.³¹ However, drug prices are not based on the costs of pill production,³² so the clinical benefits of shorter treatment courses must be clear and significant. Policy makers and providers perceive that adherence to daily oral treatment over 12 weeks will be too challenging for patients who lack stable housing, or are actively using illicit substances. In practical terms, reducing treatment length from 12 to eight or six weeks still requires a return trip to the pharmacy, as DAAs are typically dispensed in 30-day supplies. Thus, the ability to reliably achieve SVR12 with 4 weeks/28 days would be a significant breakthrough for some vulnerable patients.

The current class of drugs have similar chemical kinetics, suggesting that a new class of compounds would be needed to achieve SVR12 with only four weeks of DAA treatment.³³ Viral load at four weeks of treatment is strongly correlated with SVR12 post-treatment.³⁴ According to some experts, one bottle—and one trip to the pharmacy—is likely the physiological limit to eliminate HCV.³⁵ Results for new compounds from Gilead and Merck demonstrate that reliably successful eight-week treatments are here, particularly for patients without cirrhosis. However, 6-week treatment courses have not yet demonstrated high SVR12 rates. Researchers should continue to explore shorter treatment courses with the goal to achieve SVR12 greater than 90% with four weeks of treatment.

Glecaprevir/Pibrentasvir

A new drug application for the fixed dose, once daily combination glecaprevir/pibrentasvir (G/P; Maviret) was submitted by AbbVie in December of 2016³⁶ with FDA approval anticipated in Quarter 3 2017. Registration trials in genotypes 1-6 demonstrated uniformly high 12-week sustained virologic response (SVR12) rates of 95% with eight weeks of treatment in treatment-naïve patients without cirrhosis.³⁷ Difficult-to-treat patients with genotype 3, with and without cirrhosis, and patients with chronic kidney disease had SVR12 rates of 93-100%.³⁸ Among patients with previous DAA failure due to baseline resistance associated substitutions (RASs) SVR12 was 94% with G/P.³⁹

AbbVie has lagged in the number of patients treated behind Gilead and Merck, as well as generic formulations based on Gilead and Bristol-Meyers Squibb (daclatasvir) developed compounds in high-income countries.⁴⁰ Pricing for G/P will ultimately determine treatment uptake for this promising new treatment.

Sofosbuvir/Velpatasvir/Voxilaprevir

While AbbVie was aiming at Gilead's dominant treatments, Gilead was targeting salvage treatment for genotype (GT) 1–4 patients who had previously failed a DAA- or interferon-based regimen. The addition of a new NS3/4A protease inhibitor to sofosbuvir/velpatasvir resulted in SVR12 in 98% these patients with eight or 12 weeks of treatment (POLARIS trials).⁴¹ However, this new triple therapy, to be branded as Vosevi, has not been adequately tested in patients with decompensated cirrhosis. Mild gastro-intestinal upset, including nausea and diarrhea, were reported, but were not severe enough to discontinue treatment.

April 2017 saw the FDA approval for the use of Gilead's Sovaldi and Harvoni in adolescents aged 12-17 years old, weighing more than 35 kilograms (77 pounds) without cirrhosis or with compensated cirrhosis.⁴² Sovaldi (sofosbuvir) in combination with weight-based ribavirin is indicated for adolescents with genotypes 2 and 3, also without cirrhosis or with compensated cirrhosis. Harvoni (sofosbuvir/ledipasvir) is indicated for adolescents with genotypes 1, 4, 5 and 6, providing effectively pangenotypic treatment for this population with Gilead's products. Clinical trials for children aged 3-12 years and weighing less than 35 kilograms are ongoing.⁴³

Uprifosbuvir/Grazoprevir/Ruzasvir

Phase II data on a novel triple combination consisting of NS5B polymerase inhibitor uprifosbuvir (formerly known as MK-3682), approved protease inhibitor grazoprevir (component in Zepatier) and novel NS5A inhibitor ruzasvir (formerly MK-8408) have been presented by Merck.⁴⁴ Also known as MK3, this once daily fixed-dose combination was studied against genotypes 1, 2 and 3 in treatment durations ranging from eight weeks to 24 weeks. GT1 patients achieved SVR12 at a rate of 95% (84/88, GT1a and GT1b) with 8 weeks and 98% (45/46) with 12 weeks of treatment, respectively. GT2 had limited

response to eight weeks of treatment, with 86% (54/63) achieving SVR12. GT2 patients receiving 12 weeks of MK3 had 97% (60/62) and 100% (26/26) SVR12. Finally, GT3 patients responded with 95% (98/103) SVR12 with eight weeks, 97% (155/159) with 12 weeks and 96% (72/75) with 16 weeks. In summary, treatment duration of at least 8 weeks was sufficient to achieve high SVR12 rates with the exception of patients with genotype 2, who required 12 weeks.⁴⁵ Significantly, neither the addition of ribavirin nor the presence of compensated cirrhosis impacted treatment outcomes.

AL-335/Odalasvir/Simeprevir

Development of a novel NS5B nucleoside analogue (AL-335) in combination with odalasvir (NS5A inhibitor), with and without simeprevir (protease inhibitor Olysio), continues as the result of a partnership between Achillion and Janssen. The triple combination is known as JNJ-4178, and preliminary Phase II results in treatment-naïve and treatment-experienced patients without cirrhosis have been presented.⁴⁶ Treatment-naïve patients with genotype 1 and without cirrhosis who were treated with the triple combo for six or eight weeks resulted in 100% SVR24 (20/20 in each arm). Of patients with genotype 3 who relapsed during eight weeks of treatment, 77% achieved SVR12 when extended to 12 weeks. However, eight weeks of treatment was insufficient for GT3 patients, with only 77% (10/13) achieving SVR12 even when extended to 12 weeks on the triple combo.⁴⁷ A Phase IIb study of efficacy in non-cirrhotic patients with genotypes 2, 4, 5, and 6 is ongoing.⁴⁸

Injectables

Data on a proof-of-concept injectable micro-RNA (miRNA) based treatment from Merck was expected at the 67th Meeting of the American Association for the Study of Liver Diseases (AASLD) in 2016; however, the poster was withdrawn prior to the conference.⁴⁹ The market viability of injectable treatments based on difficult-to-produce miRNA technology is questionable given the efficacy of current oral treatments, and the future development of this treatment route is unclear.

Generic DAAs

Real-world data on generic DAAs, most extensively sofosbuvir and daclatasvir in fixed-dose combination, have consistently demonstrated SVR12 rates comparable to those of drugs manufactured by originator companies (REDEMPTION trials).⁵⁰ Patients accessing generics manufactured in Bangladesh, China, and India achieved an average SVR12 rate across all genotypes. As with branded sofosbuvir/daclatasvir, GT3 continued to be difficult-to-treat, achieving an SVR12 rate of only 94%. National health ministries should implement generic-based treatment for everyone wherever voluntary licenses are registered. Unfortunately, registration with national regulatory bodies continues to be a major barrier to treatment uptake in low- and middle-income countries, with expanded registration being a top priority among global treatment activists. Real-time data on registration is available at mapCrowd.org, a collaboration between Médecins du Monde and Treatment Action Group.

Real World Data in People Who Use Drugs

Transmission of HCV among people who inject drugs continues to be the main driver of the global epidemic. Stigmatization, discrimination and myths that active drug users cannot adhere to daily treatment regimens have resulted in treatment restrictions and other policies that further marginalize those we need to engage the most. However, post-marketing studies of DAA treatment in active drug users and those in opioid substitution therapy (OST) demonstrate that HCV cure rates comparable to those in clinical trials can be achieved among people who inject drugs.

The SIMPLIFY trial, a Phase IV open-label multicenter international trial of sofosbuvir/velpatasvir in people with injection drug use in the prior six months and compensated liver disease, resulted in 94% of participants achieving SVR12 (96/99; four participants were lost to follow up).⁵¹ Participants were recruited from March through October 2016 with no relapse or reinfection observed to date.

The C-EDGE CO-STAR trial, a Phase III randomized double blind parallel group trial of grazoprevir/elbasvir in patients in OST for minimum of three months, consisted of two arms: 12 weeks of treatment versus placebo for 12 weeks followed by 12 weeks of treatment (starting at week 16).⁵² Both arms achieved high SVR12 rates: 96% (189/198) and 97% (85/88), respectively. Follow up continued to SVR24, with 96% (175/186) and 97% (82/85) of patients maintaining cure. The six reinfections which occurred are equivalent to 3.4 per 100 person years.

These data support treatment for everyone without restriction.

Finding people with chronic HCV infection: diagnostics for elimination

Globally, less than 5% of individuals chronically infected with viral hepatitis have been diagnosed, and estimates of the global burden of chronic HCV are 71–80 million individuals (POLARIS Observatory data).⁵³ Modeling studies indicate that 5–10% of the global infected population must be treated each year from 2018–2030 to achieve the targeted 90% reduction in viral hepatitis incidence and 65% reduction in associated mortality. To screen and diagnose the hundreds of millions of individuals at risk of infection, diagnostic technologies and algorithms will need to be rethought, streamlined, and implemented across a range of settings outside of tertiary hospital or even primary care community clinic sites. To meet this tremendous need, technologies will need to be affordable, provide results in a single visit, sufficiently inform regimen choice, and confirm cure.

As concisely described by John Dillon, MD, Professor of Hepatology and Gastroenterology, University of Dundee, the minimal inputs for confirmed cure of HCV are blood for an RNA confirmatory test, DAAs, and blood to confirm SVR12. Ideally, blood could be collected as a dried blood spot. Building clinic infrastructure and deploying new technologies appropriate to acquire the blood inputs are critical priorities for the next three to five years. It is particularly important to deploy low-cost solutions in resource-limited settings across high-, middle-, and low-income countries, specifically where people who inject drugs receive harm reduction, opioid substitution, and other services; in jails and prisons; to migrants regardless of legal status; and where pregnant women receive care. In high-income countries, including the U.S., emergency rooms have been shown the potential of capturing new infections, particularly among young people outside of the baby boomer birth cohort (1945–1965 in the U.S.),⁵⁴ but lack both the payer mechanisms and clinic flow to inform and link infected individuals to care in a timely manner. Rapid point-of-care RNA assays could fill critical gaps in screening programs and provide opportunities to effectively bring more into treatment.

The only point-of-care rapid diagnostic HCV antibody test available in the field and recognized as reliable by regulatory bodies is the Oraquick test from OraSure. Although not yet WHO prequalified, the assay is CE marked (Conformité Européenne; accepted as quality assured in the European Union) and provides results with both capillary blood and oral swabs. However, with pricing ranging from USD\$8 to over USD\$10, price remains a barrier to wide-scale deployment in limited resource settings. The work of Andrew Hill, University Liverpool, has shown that generic DAAs can be produced for less than USD\$200 per treatment course, including 50% mark up.⁵⁵ In countries with voluntary licensing, generic prices continue to fall, approaching Hill's model. Ironically in those circumstances, pre- and post-treatment diagnostics can cost USD\$500–600,⁵⁶ with little or no support for patients. As a result, out-of-pocket diagnostic costs are often a greater barrier to treatment access than the price of DAAs.

The Foundation for Innovative New Diagnostics (FIND), the leading non-profit organization advocating for appropriate diagnostics in low- and middle-income countries, has developed target product profiles (TPPs) for HCV diagnostics. The following table compares point-of-care tests currently in the field and in the pipeline to FIND's TPP (see Table 2).

Table 2. Target Product Profiles for HCV Diagnostics

Assay Name	Optimal spec	Minimal spec	Assay TPP Specification Result						
			Xpert HCV RNA	Truenat HCV	Architect core Ag	Realtime HCV	Alere q RNA	HCV Qual/Quant	HCV RNA POC
Developer/manufacturer			Cepheid	Molbio/bigTech	Abbott	Abbott	Alere/SD	Roche	Genedrive
Registrational status			Approved	Pipeline	Approved	Approved	Pipeline for HCV	Approved	Pipeline
Target users	Community workers	Health-care workers	Minimal	Optimal	Minimal	Minimal	Minimal	Minimal	Optimal?
Setting	Community centers	District hospitals (II)	POC, but somewhat centralized	Optimal	Minimal	Minimal	Optimal	Minimal	Both
Analytical sensitivity	200 IU/mL	1,000–3,000 IU/mL	Minimal	?	Minimal	Minimal	?	Optimal for quantitative	Yes
Diagnostic sensitivity	>99%	>98%	Minimal	?	Minimal	Minimal	?	Optimal	TBD
Polyvalency	Platform allows HCV, HBV, HIV tests	Platform allows HCV, HBV, HIV tests	Yes	HIV	HIV	HIV, HCV genotyping	HIV	HIV	TBD
Quantitation	Quantitative	Qualitative	Optimal	Optimal	Minimal	Optimal	Optimal	Both	Approximate quantitative results
Specimen type	Capillary blood	Venous blood/plasma	Both	Both	Both	Both	Both	Both	Both
Steps	<2	2	Cartridge based	?	Cartridge based	Cartridge based	Cartridge based	1, precision pipetting required	~4
Time to result	<15 min	<60 min	105 min	60 min	36 min	5+ hrs (batch processing)	?	5-8 hrs (batch processing)	<90 min
Instrument cost	<2,000 USD	<20,000 USD	17,000 USD	9,000 USD	?	207,000 USD	?	150,000 USD	?
Assay price	<5 USD	<15 USD	<20 USD	14 USD	25–50 USD	13–35 USD	15–25 USD?	Depends on country	?

POC: point-of-care.

Courtesy of FIND⁵⁷, MSF Access Campaign⁵⁸, Genedrive⁵⁹.

HCV TREATMENT RECOMMENDATIONS

Next steps: getting where we want to go

Elimination of viral hepatitis C as a public health concern is feasible. Although we currently lack reliable, affordable diagnostics and nonspecialist provider capacity, those can be developed with time and commitment. Curative oral therapies continue to improve, and, as disease progression and sobriety restrictions fall, scaled up treatment and competition will contribute to driving prices down for branded and generic drugs.

Decades of research into the virus has yielded a promising vaccine candidate (see Box: A vaccine for HCV?) and real-world data on treatment adherence and shortened treatment duration suggests that it is possible to further cut costs and improve the efficiency of public health strategies. Implementation science on how to intervene successfully to prevent reinfection and support the most vulnerable patients—active injection drug users, the homeless, and other marginalized communities—will be critical in this phase of the fight.

Concrete, concerted action is needed to move forward:

- National governments must develop HCV action plans in consultation with affected populations, especially people who use drugs, people co-infected with HIV, and women;
- National governments must use every available legal tool, including TRIPS flexibilities, compulsory licenses, and patent opposition, to secure affordable DAAs;
- Generic producers and diagnostics manufacturers must partner to develop bulk procurement proposals in low- and middle-income countries;
- Public and private payers must make multi-year commitments to fund HCV diagnosis and treatment;
- Diagnostic technologies and algorithms will need to be rethought, streamlined, and implemented across a range of settings outside of tertiary hospital or even primary care community clinic sites;
- More options for point-of-care RNA assays are needed to fill critical gaps in screening programs and facilitate putting more patients on treatment.
- Diagnostic technologies will need to be affordable for low- and middle-income countries and provide results in a single visit, sufficiently inform regimen choice, and confirm curative rates in patients;
- Sustainable funding for vaccine research to show efficacy in people at risk for HCV infection because they inject drugs; the ability to elicit immune response in individuals living with HIV who are not at high risk for HCV infection; and safety in combination with HIV vaccine administration in healthy volunteers;
- Researchers must pursue four-week treatment courses that match current SVR12 rates of 90% or greater across genotypes, levels of disease severity, and comorbidities and infections, including HIV/HCV co-infection.

Science has brought us to the brink of winning the biochemical battle with HCV. How far and how fast we move towards elimination will depend on evidence-based solutions to battles outside of the liver—the incoherence between intellectual property and the human right to health, the lack of global funding streams for viral hepatitis, the deadly war against drug users, and the need to galvanize global demand for treatment for all.

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A vaccine for HCV?

The world's first recombinant vaccine was the hepatitis B vaccine, based on hepatitis B surface antigen, and a half dozen commercial vaccines exist for hepatitis A. However, a prophylactic HCV has eluded researchers. That may be about to change.

Although HIV is a more extreme example, HCV can also be considered a master virus, supremely adapted to stay one step ahead of the human immune system. Rapidly mutating and ten times more variable than HIV in its genotypic subtypes, HCV elicits a weak immune response,⁶⁰ resulting in poor viral control and chronic infection of hepatocytes (liver cells) in most. Approximately 25% of individuals exposed to HCV spontaneously clear the virus. People who inject illicit drugs and other high-risk groups can be repeatedly exposed to HCV. Some individuals in high-risk groups infected are repeatedly able to clear the virus again and again without treatment and exhibit a broadening of their adaptive antibody-mediated immune response with repeated exposure to HCV.

Evidence from people who control HCV infection and primate studies suggests a potential role for broadly neutralizing antibodies (bNAbs) in effective vaccine design for HCV. bNAbs for both HIV and HCV have been identified, and how to induce bNAbs is being studied for vaccine development. However, the precise interaction of antibody and T-cell-mediated responses in protecting against infection are unknown at this time. bNAbs targeting HCV envelope proteins have been tested in healthy people.⁶¹

Further back in the pipeline, the only vaccine ever tested in high-risk individuals is an HCV prophylactic vaccine (Ad Ch3 NS/MVA NS) originated by Okairos and that is now being developed in collaboration with GlaxoSmithKline. Results are pending from Phase II trials in three groups: for efficacy in people at risk for HCV infection because they inject drugs (NCT01296451); for ability to elicit immune response in individuals living with HIV (NCT02568332) who are not at high risk for HCV infection; and for safety in combination with HIV vaccine administration in healthy volunteers (NCT02362217). These results will determine whether this candidate vaccine is effective on its own or needs to be combined or enhanced with vaccines that generate bNAbs against envelope proteins.

The high cost of curative treatments will continue to limit treatment access in the near term, and cost-driven concerns about reinfection, particularly among people who inject drugs and men who have sex with men, present considerable challenges to advocates for universal access and treatment as prevention. Primary prevention through an affordable, effective vaccine could be our most powerful tool for defeating the virus. Data generated in this upcoming year will tell us if we're one step closer to adding a preventative vaccine to our HCV toolkit.

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