Overview of New Treatments for Hepatitis C Virus: Moving Towards a Public Health Agenda

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AIDS acquired immune deficiency syndrome
ART antiretroviral therapy
ARVs antiretrovirals
DAAs direct-acting antivirals
DCV daclatasvir
EMA European Medicines Agency
EU European Union
FDA Food and Drug Administration
FDC fixed-dose combination
G genotype; as in genotype 1 (G1), genotype 2 (G2), and genotypes 3, 4, 5 and 6
HCC hepatocellular carcinoma
HCV hepatitis C virus
HIC high-income country
HIV human immunodeficiency virus
LIC low-income country
LMIC low-and middle-income countries
MIC middle-income country
MSM men who have sex with men
NSP needle syringe programme
OST opioid substitution
PEG-IFN pegylated interferon
PK pharmacokinetic
PWID people who inject drugs
RAVs resistance-associated variants
RBV ribavirin
RLS resource limited setting
SOF sofosbuvir
SVR sustained virologic response
SVR-12 sustained virologic response, 12 weeks after treatment completion; equivalent to cure
US United States
WHO World Health Organization
Worldwide, an estimated 185 million people have been infected with hepatitis C virus (HCV); 170 million are chronically infected. The highest prevalence of hepatitis C is found in middle-income countries (MICs).

Hepatitis C is blood borne. It is transmitted through unscreened organs, blood and blood products; via injection drug use with shared needles, syringes, filters and other paraphernalia; in medical or dental settings where infection control procedures are inadequate; by tattooing with shared equipment, ink and inkwells and sexually, especially between HIV-positive men who have sex with men.

HCV can be vertically transmitted. Vertical transmission incidence ranges from 3% to 10%; untreated HIV coinfection increases the risk. Currently, there is no way to reduce the risk of, or prevent vertical HCV transmission.

1. Hepatitis C: Natural History

| Hepatitis C becomes chronic in 75% of adults, and 80% of children. Others will spontaneously clear their infection, usually within months. Reinfection is possible in people who spontaneously cleared HCV, or were successfully treated. |
| Consequences of untreated chronic HCV infection include depression, cardiovascular and autoimmune disorders and liver scarring. Liver damage is accelerated in males, and by HIV coinfection, alcohol intake and other factors, especially duration of infection. In otherwise healthy children, progression to cirrhosis rarely occurs during the first decade of infection. After 20 years of infection, 16% of adults develop cirrhosis; this increases exponentially to 40% after 30 years. People with cirrhosis are at risk for hepatocellular carcinoma and liver failure. Each year, 700,000 people die from HCV-related causes. |

Hepatitis C becomes chronic in ~75% of infected adults; the remaining 25% usually clear infection within the first 3 to 12 months after initial infection, an outcome known as spontaneous viral clearance.1 People can become reinfected with hepatitis C after spontaneous viral clearance or successful treatment.

Although it is often initially asymptomatic, untreated, chronic hepatitis C infection can wreak havoc outside of the liver, as well as causing liver damage. Up to 74% of people with chronic HCV suffer from extrahepatic manifestations—even in the absence of serious liver damage, including depression, fatigue, anxiety, autoimmune and dermatological disorders, increased risk for stroke and lymphoma, and cardiovascular, neurocognitive, central nervous system, renal and bone damage.2,3,4,5,6,7
Hepatitis C may contribute to non-liver related mortality. People with hepatitis C are dying two decades earlier from non-liver related illness (such as cardiovascular disease, respiratory failure, hypertension and diabetes) than their uninfected peers.5

Spontaneous viral clearance occurs in 20% of children with HCV infection.9,10 Chronic hepatitis C is usually asymptomatic in children. During the first decade of infection, progression to cirrhosis and end-stage liver disease is rare among otherwise healthy children.11,12,13

Over time, chronic hepatitis C causes liver scarring. The progression of liver damage is not linear, and it varies, by host and viral factors that include male sex, HIV status, coinfection with hepatitis B virus, alcohol intake, obesity, type 2 diabetes, steatosis (fatty liver) and aging. Duration of infection accelerates liver damage: after 20 years of HCV infection, the estimated prevalence of cirrhosis is 16%; at 30 years, it increases to 40%.14

People with cirrhosis are at risk for hepatocellular carcinoma (HCC) at the rate of 1% to 5% per year, and liver failure at the rate of 3% to 6% per year. Each year, 700,000 people die from these HCV complications.15 As of 2012, cirrhosis of the liver was the tenth leading cause of death in lower-middle-income countries, and liver cancer was the ninth leading cause of death in upper-middle-income countries.16,17 In certain high-income countries, where access to antiretroviral therapy (ART) for HIV is widespread, more people are now dying from HCV complications than AIDS.18,19,20

2. Hepatitis C Genotypes and Their Global Distribution

There are seven known HCV genotypes—each with dozens of subtypes.21,22 The high genetic variability of hepatitis C virus (>30% nucleotide difference between genotypes, 15% to 30% nucleotide difference among subtypes) has made it difficult to develop universally effective vaccines and treatment.22 In fact, the type, duration and outcome of HCV treatment may vary according to genotype—and sometimes subtype.

Globally, genotype 1 predominates (46.2%, or 83.4 million cases), followed by genotype 3 (30.1%, or 54.3 million cases), genotype 2 (9.1%, or 16.5 million cases), genotype 4, (8.3%, or 15 million cases), genotype 6 (5.4%, or 9.8 million cases), and genotype 5 (<1%, or 1.4 million cases); there is a single known case of genotype 7.21 Mixed infections, with more than one hepatitis C genotype or subtype have been reported in people with multiple exposures, such as transfusion and blood product recipients, dialysis patients and people who inject drugs (PWID).23,24
Figure 1. Global Distribution of HCV Genotypes


Pan-genotypic hepatitis C treatment regimens will simplify scale-up, procurement and delivery of HCV treatment. Many direct-acting antivirals (DAAs) have been developed primarily for genotype 1; some are effective against multiple HCV genotypes. DAAs are less effective for people with genotype 3 and cirrhosis. Safety and efficacy data in genotypes 4, 5 and 6 are limited to in vitro studies and small numbers of study participants.

Table 1. Global Distribution of HCV Genotypes, By Income Classification

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>%, Low-Income Countries</th>
<th>%, Lower Middle-Income Countries</th>
<th>%, Upper Middle-Income Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.3</td>
<td>30.7</td>
<td>60.6</td>
</tr>
<tr>
<td>2</td>
<td>8.3</td>
<td>6.7</td>
<td>10.8</td>
</tr>
<tr>
<td>3</td>
<td>25.4</td>
<td>44.4</td>
<td>15.9</td>
</tr>
<tr>
<td>4</td>
<td>18.5</td>
<td>17.7</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>5.9</td>
<td>0.2</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>1.7</td>
<td>0.4</td>
<td>10.7</td>
</tr>
</tbody>
</table>

3. HCV Treatment: Goals and Evolution

The goal of HCV treatment is cure (also referred to as sustained virologic response [SVR]). Being cured reduces the risk for liver-related and all-cause morbidity and mortality.

The standard of care for HCV has improved dramatically. Pegylated interferon and ribavirin—a partially effective regimen with potentially debilitating side effects— is being replaced by safe, tolerable oral direct-acting antivirals (DAAs). These drugs have cured >90% of people in clinical trials, in only 12 weeks. DAA regimens are suitable for resource-limited settings—where HCV is rampant, since these drugs simplify treatment procurement and delivery, improve HCV treatment outcomes, and could save millions of lives.

There are four classes of direct-acting antivirals: protease inhibitors, non-nucleoside polymerase inhibitors, nucleoside/tide polymerase inhibitors and NS5A inhibitors, each with different characteristics. Currently, two fixed-dose combinations (sofosbuvir/ledipasvir and Ombitasvir/paritaprevir/ritonavir plus dasabuvir), and three DAAs (sofosbuvir, a nucleotide polymerase inhibitor, daclatasvir, an NS5A inhibitor and simeprevir, an HCV protease inhibitor) have been approved in high-income countries.

The goal of hepatitis C treatment is to cure the virus, an outcome referred to as sustained virologic response (SVR-12; no hepatitis C virus can be detected in a blood sample 12 weeks after finishing treatment). SVR is durable; after being cured, some patients have been followed for two decades and remain virus-free. Being cured reduces the risk for liver-related and all-cause morbidity and mortality, including from cardiovascular disease, at all stages of liver disease, and regardless of HIV status.

Until recently, hepatitis C was treated with 6 to 12 months of weekly pegylated interferon (PEG-IFN) injections, and twice-daily ribavirin (RBV) tablets—a partially effective regimen, with side effects that could be debilitating and even life threatening. The toxicity, complexity, monitoring requirements, and limited efficacy of PEG-IFN-based hepatitis C treatment make it undesirable—especially for resource-limited settings (RLS).

The interferon-free HCV treatment era began in 2011. Regulatory agencies approved the first HCV protease inhibitors (initially used with PEG-IFN and RBV), and researchers demonstrated proof-of-concept for curative oral therapy. Since then, numerous trials of interferon-free, oral direct-acting antiviral (DAA) regimens have reported cure rates ≥ 85% regardless of HCV genotype—many in only 12 weeks. By 2014, several options for
HCV treatment became available-- primarily in HICs-- where hepatitis C treatment is shifting to DAA combinations.

**Figure 2. Evolution of HCV Treatment**

![Graph showing the evolution of HCV treatment from 1998 to 2017](http://pennstatehersheygireport.org/2013/06/27/new-developments-in-the-rapidly-evolving-landscape-of-hepatitis-c-therapy/) (did not request/obtain permission since I found it while searching for copyright-free images)
Table 2. DAAs: Regulatory Approval in the European Union and the United States

<table>
<thead>
<tr>
<th>DAA or Regimen</th>
<th>Class, formulation</th>
<th>Genotypes</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>Nucleotide polymerase inhibitor</td>
<td>1,2,3,4 (less data in genotypes 5 and 6)</td>
<td>2013 (EU and US)</td>
</tr>
<tr>
<td>Used with PEG-IFN and RBV or RBV alone; simeprevir or daclatasvir, with or without RBV, for 12 or 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Protease inhibitor</td>
<td>1 and 4</td>
<td>2013 (US) 2014 (EU)</td>
</tr>
<tr>
<td>Used with: PEG-IFN and RBV, or sofosbuvir, with or without RBV, for 12 or 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>NSSA inhibitor</td>
<td>1,2,3,4 (no data in genotypes 5 and 6)</td>
<td>2014 (EU) Submitted in 2015 (US)</td>
</tr>
<tr>
<td>Used with PEG-IFN and RBV or sofosbuvir, with or without RBV, for 12 or 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>FDC: nucleotide polymerase inhibitor and NSSA inhibitor</td>
<td>1,3,4 and 6</td>
<td>2014 (EU and US)</td>
</tr>
<tr>
<td>Used with or without RBV, for 8, 12 or 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir plus dasabuvir</td>
<td>FDC: NS5A inhibitor, ritonavir-boosted HCV protease inhibitor used with a non-nucleoside polymerase inhibitor</td>
<td>1 and 4</td>
<td>2014</td>
</tr>
<tr>
<td>Used with or without RBV, for 12 or 24 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DAA regimens are shorter, safer, better tolerated and significantly more effective across host and viral factors than PEG-IFN and RBV. These regimens require minimal monitoring during and after treatment, so they are far simpler to administer and undergo than interferon-based treatment.

Although other approaches to treating hepatitis C virus—such as micro-RNA and host-targeting agents—are under study, none have been approved. There are four classes of
DAAs: protease inhibitors, non-nucleoside polymerase inhibitors, nucleoside/tide polymerase inhibitors and NSSA inhibitors.

### 3.1 HCV Protease Inhibitors

In 2002, BILN-2061, the first HCV protease inhibitor entered human trials; it was discontinued for cardiotoxicity shortly thereafter. The first approved DAAs were HCV protease inhibitors (boceprevir and telaprevir). These drugs were used as part of response-guided therapy with PEG-IFN and RBV. Although they increased SVR (from approximately 45% to approximately 70%) in genotype 1, boceprevir and telaprevir were associated with serious adverse events and added to cost and complexity of treatment.

Now, once-daily HCV protease inhibitors (simeprevir and paritaprevir/ritonavir) are part of all-oral DAA combinations for HCV genotypes 1 and 4. HCV protease inhibitors are less effective for genotype 1a, due to a lower resistance barrier. Some protease inhibitor-based regimens require ribavirin for genotype 1a, or are used only for genotype 1b.

Most HCV protease inhibitors are not pan-genotypic—they are not sufficiently effective against genotype 3. But it may be possible to overcome this Achilles heel by combining them with other DAAs. Merck is exploring this strategy by adding sofosbuvir to their grazoprevir/elbasvir (HCV protease inhibitor and NS5A inhibitor fixed-dose combination (FDC)).

HCV protease inhibitors have a propensity for drug-drug interactions and cannot be co-administered with several commonly used medications, including some HIV antiretrovirals (ARVs).

Newer protease inhibitors may be more potent overall, have a higher genetic barrier to drug resistance, and activity against drug-resistant strains of hepatitis C. The protease inhibitors currently in phase 2, ABT-493 (under study as an FDC with ABT-530, AbbVie’s NS5A inhibitor) and Gilead’s GS 9857 (under study sofosbuvir/velpatasvir [nucleotide polymerase inhibitor/ NS5A inhibitor] FDC), may be more effective against genotype 3.

### 3.2 HCV Non-Nucleoside Polymerase Inhibitors

The potency and resistance barrier of drugs in this class range from low to moderate; many have been discontinued for toxicity or lack of efficacy. Most non-nucleoside polymerase inhibitors are twice-daily drugs, primarily active against genotype 1. Although non-nucleosides contribute to regimen efficacy for HCV genotype 1, the need for, and future of drugs from this class is unclear.39,40

### 3.3 HCV Nucleoside/tide Polymerase Inhibitors

Sofosbuvir, the only approved nucleotide polymerase inhibitor, has the best features of this class: multi or pan genotypic activity, potency and high resistance barrier, low propensity
for drug-drug interactions, and once daily dosing. Although HCV nucleotides have great potential, toxicity or lack of efficacy has hindered their development in the past.

Fortunately there are other nucleotide polymerase inhibitors in early-stage development: Merck’s uridine analog MK-3682 (formerly IDX 21437) is in phase 2. Achillion’s uridine analog polymerase inhibitor, ACH-3422, is in phase 1. Janssen’s AL-335, a uridine analog, is in phase I, and AL-516, a purine analog in pre-clinical development.

3.4 HCV NS5A Inhibitors

HCV NS5A inhibitors are a completely novel drug class. Many—but not all—NS5A inhibitors are pan-genotypic (although they have been studied in only a handful of people with HCV genotypes 5 and 6). These drugs are once daily; their propensity for drug-drug interactions varies.

NS5A inhibitors are potent, yet most have a low barrier to resistance (although some candidates in early develop may have a higher barrier to, or activity against, resistant virus). Pretreatment NS5A resistance does not always preclude being cured, especially when these drugs are combined with potent DAAs. But for people who are not cured, longevity and impact of NS5A resistance on HCV treatment options are unclear. With this class, additional research is needed to forestall or overcome drug resistance.

4. HCV: Target Product/Regimen Profile

The characteristics of an ideal regimen include safety and universal efficacy (cure rate of ≥85% across all populations, including during pregnancy and nursing, in paediatrics and people with cirrhosis; HIV coinfection; and other common comorbidities). Treatment must be simple, with minimal safety and efficacy monitoring, and convenient—preferably once daily—so it is easy to administer and undergo.

Data is needed on DAAs during pregnancy and nursing; the first paediatric studies are underway. Despite gaps in knowledge and limitations of currently available DAAs, they have many of the characteristics needed to address HCV globally.

Due to the predominance of HCV genotype 1—especially in high-income countries—DAA development has been focused on it. All DAA classes work against genotype 1—although most are more effective against genotype 1b than genotype 1a. The most common strategy
for treating HCV genotype 1 is using DAAs from multiple classes, to shorten treatment and increase cure rates. Although cure rates in trials combining DAAs from 3 classes have topped 95%, those who are not cured may be left with few options.

Pan genotypic strategies are becoming more desirable, due to the global focus on HCV. Currently, sofosbuvir is the optimal backbone for a first-line regimen, since it is pan-genotypic, can be used in cirrhosis, has a low propensity for drug-drug interactions, and a high resistance barrier. Pairing it with a pan-genotypic NS5A inhibitor obviates pre-treatment genotypic testing, and will minimize safety and efficacy monitoring during and after treatment. But the weakness of NS5A inhibitors is baseline or emergent drug resistance that may limit their effectiveness.41,42,43,44,45 Candidates in phase II development (AbbVie’s ABT-530, Achillion’s ACH-3102, and Merck’s MK-8408) are purported to be more potent, and active against drug resistant virus.

The ideal DAA regimen for HCV treatment scale up does not exist—yet (especially in regard to affordability an use in pregnancy, nursing and paediatrics). These characteristics are: Safe and Tolerable; preferably ribavirin-free; minimal pre-treatment assessment or safety/efficacy monitoring needed;

- Effective and Durable: potent, with high genetic barrier and SVR ≥85%, regardless of age, treatment experience, HIV status, HCV genotype, liver disease severity, kidney disease;
- Universal: pan-genotypic; safe for use during pregnancy and nursing, and in pediatrics, HIV/HCV, and cirrhosis;
  - In paediatrics, age appropriate formulation, scored, dispersible tablets, usable across broad weight bands
- Simple and convenient: manageable drug-drug interactions with ARVs, opioid substitution treatment (OST) and other commonly-used medications; fixed duration (≤12 weeks); minimal requirements for pre-treatment assessment and safety/efficacy monitoring during and after treatment; once-daily (FDC preferred), without food requirement;
- Stable at high and low temperatures
- Affordable.

Table 3. Target Product Profile: Ombitasvir/paritaprevir/ritonavir plus dasabuvir, Daclatasvir, Sofosbuvir, Sofosbuvir/ledipasvir and Simeprevir

**REGIMEN, STATUS, SPONSOR (s)**

**UNIVERSAL and SAFE**
Assumptions: DAAs or regimens are well tolerated, as evidenced by low discontinuation rates in clinical trials (<5%). They are safe--but less effective-- for people with compensated cirrhosis, especially in G3. No data during pregnancy and nursing, or pediatrics

### Pan-genotypic

<table>
<thead>
<tr>
<th>Data in HIV/HCV</th>
<th>Hepatic impairment</th>
<th>Renal impairment</th>
<th>≤12 weeks for all</th>
<th>Propensity for DDIs</th>
<th>QD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ombitasvir/paritaprevir/ritonavir and dasabuvir</strong> APPROVED in EU and US AbbVie</td>
<td>G1 and G4 only</td>
<td>SVR is comparable</td>
<td>No dose adjustment for mild, moderate or severe renal impairment</td>
<td>NO</td>
<td>HIGH</td>
</tr>
<tr>
<td><strong>Daclatasvir</strong> APPROVED in EU; submitted in US BMS</td>
<td>Pan-genotypic in vitro; studied in G1, G2, G3 and G4</td>
<td>SVR is comparable</td>
<td>No dose adjustment for mild, moderate or severe renal impairment</td>
<td>?</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Sofosbuvir</strong> Gilead Sciences APPROVED in EU and US</td>
<td>YES</td>
<td>YES, SVR is comparable</td>
<td>No dose adjustment for mild, moderate or severe renal impairment</td>
<td>Varies</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Sofosbuvir/ledipasvir</strong> APPROVED in EU and US Gilead Sciences</td>
<td>NO; G1, 3, 4 and 6</td>
<td>YES, SVR is comparable</td>
<td>No dose adjustment for mild, moderate or severe renal impairment</td>
<td>Varies</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**SIMPLE**

**EFFECTIVE**
SVR >85%

**COMMENTS**
Complex, subtyping required, RBV needed in some populations
Optimal duration with sofosbuvir unclear for G3 and cirrhosis; RBV may be needed; contraindicated in pregnancy; no in vivo data in G5 and G6
Used with RBV in G2 and G3; very limited in vivo data in G5 and G6; duration depends on genotype and regimen
RBV required in G3; under study in G2; no in vivo data in G5; limited in vivo data in G6
### 5. HCV Treatment Criteria and Strategies

Each year, 700,000 people die from complications of HCV, a curable virus. HCV treatment has individual and public health benefits. Current HCV treatment rates are low, ranging from 1% to <5%, in part due to the high price of DAAs. This has led to restrictions, and prioritizing people with the most advanced liver disease—a strategy that will reduce HCV-associated illness and death, but won’t stop the epidemic from spreading.

When combined with primary prevention, DAAs increase feasibility of HCV treatment-as-prevention (TasP). Modest increases in HCV treatment rates among people who inject drugs could dramatically reduce prevalence in this population.

The same steps that have led to drastic reductions in the price of HIV antiretrovirals can be used with DAAs. In fact, they can be mass-produced profitably, and remain affordable. Diagnostics and monitoring can also be simplified, leading to a total cost of less than US$ 500 to diagnose and cure hepatitis C.

A public health approach can be used for global HCV treatment scale up: selecting a universal first-line regimen that minimizes safety and efficacy monitoring.
To stem an annual death toll of 700,000 people, global HCV treatment scale-up must be prioritized.15 HCV treatment has the potential to provide vast individual and public health benefits. But high prices have limited access to HCV treatment—even in high-income countries—to people with advanced liver disease (METAVIR F3 and F4). In the United States, public and private payers have imposed non-evidence based restrictions (such as requiring 3 to 12 months of abstinence from drugs and alcohol), and forged exclusivity agreements with pharmaceutical companies that limit clinical decision-making.46,47,48,49 In Europe, high DAA prices have led France to threaten taxation for costly HCV drugs, delayed their approval in the United Kingdom, or limited access in Spain.50,51,52

If DAAs are to stem HCV-related morbidity and mortality in the coming years, and reduce the global burden of HCV infection, current HCV treatment rates of 1% to <5%—must increase.53,54,55 Treating people with fibrosis (METAVIR SCORE: >F2) will reduce HCV-associated morbidity and mortality—but unless people with less liver damage (METAVIR SCORE: F0 and F1) are treated, the epidemic will continue to spread.56

Table 4. Current HCV Treatment Criteria57,58,59

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection World Health Organization April 2014</td>
<td>All adults and children with chronic HCV infection, including PWID, should be assessed for antiviral treatment...patients with advanced fibrosis and cirrhosis (METAVIR stages F3 and F4) should be prioritized for treatment as they are at higher risk of developing cirrhosis and hepatocellular carcinoma. If resources permit, then persons with less advanced fibrosis (METAVIR stages F1 and F2) could also be considered for treatment.</td>
</tr>
<tr>
<td>EASL Recommendations on Treatment of Hepatitis C 2014 European Association for the Study of the Liver (EASL) April 2014</td>
<td>All treatment-naïve and –experienced patients with compensated disease due to HCV should be considered for therapy. Treatment should be prioritized for patients with significant fibrosis (METAVIR Score F3 to F4). Treatment is justified in patients with moderate fibrosis (METAVIR Score F2). In patients with no or mild disease (METAVIR Score F0-F1), the indication for, and timing of therapy can be individualized.</td>
</tr>
<tr>
<td>Recommendations for Testing, Managing and Treating Hepatitis C American Association for the Study of Liver Diseases/ Infectious Diseases Society of America (AASLD/IDSA) March 2015</td>
<td>Treatment is recommended for patients with chronic HCV infection. Immediate treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C.</td>
</tr>
</tbody>
</table>
In Egypt, home of the world’s highest HCV prevalence (14.7%), modeling the impact of different eligibility criteria on life-years saved found that limiting treatment to people with advanced liver disease (METAVIR SCORE: F3 and F4) was most effective—but the model did not consider the annual infection rate, or the impact of these restrictions on transmission.60

Affordable DAAs increase the appeal and feasibility of HCV treatment-as-prevention (TasP). Primary prevention measures must be scaled up in tandem with TasP if it is to be fully effective. In Egypt, HCV is still spreading despite a national treatment program; scaling up infection control to prevent healthcare- and household-associated exposures is as important as providing widespread HCV treatment.61 For people who inject drugs—the highest-prevalence population—DAAs and high coverage opioid substitution treatment (OST) and needle and syringe programmes (NSP) — are essential for reducing HCV prevalence (PWID).62

Scaling up HCV treatment access --and rates--among PWID could dramatically reduce prevalence in this population (estimated at 67%, or at least 10 million people).63 Martin and colleagues modeled the impact of DAA treatment scale-up, based on a 90% SVR rate, HCV prevalence and current treatment rates among people who inject drugs in three cities. In Edinburgh (where prevalence among PWID is currently 25%, and 7/1000 are treated annually) and Melbourne (where prevalence is 50%, and 3/1000 are treated annually). In just 15 years, prevalence among people who inject drugs could be halved, by scaling up the annual treatment rate in these cities to 22/1000. In Vancouver, where HCV prevalence among PWID is 65% and 5/1000 are treated annually; treating 98/1000 would halve it in 15 years. Prevalence could be reduced to 30% in Vancouver and less than 5% in Edinburgh and Melbourne by treating 80/1000 annually.64

5.1 DAA Pricing and Access
Although there are several barriers to universal HCV treatment access, high DAA prices are the greatest obstacle. The same steps that have led to a 99% drop in the price of antiretroviral therapy for HIV-demand creation, community mobilization, treatment literacy, generic competition, economies of scale, and improved procurement of raw materials manufacturing processes are possible for HCV treatment.65,66
DAAs that simplify diagnostics and limit monitoring requirements can be mass-produced affordably, and sustainably, according to Hill and colleagues, who compared chemical structure and synthesis complexity, molecular weight and dosing between antiretroviral agents and certain DAAs, and added margins for formulation and profit. DAAs were prioritized by safety and efficacy; these were ribavirin, sofosbuvir (nucleotide polymerase inhibitor), the NS5A inhibitors daclatasvir, ledipasvir and elbasvir (formerly MK-8742; currently in phase 3) and the protease inhibitor grazoprevir (formerly MK-5172; currently in phase 3). Regimens were priced at: US $118 (12 weeks of grazoprevir/elbasvir); US $121 (12 weeks of sofosbuvir/daclatasvir); US $129 to $193 (8 or 12 weeks of sofosbuvir/ledipasvir), US$ 149 to $298 (12 or 24 weeks of sofosbuvir and ribavirin).\textsuperscript{67,68}

As a next step, the researchers determined need for, type, and frequency of monitoring based on safety data from clinical trials (a complete blood count and other routine clinical chemistry tests, such as liver enzyme and creatinine levels, once before and once during treatment). They selected an antigen test (used for diagnosing HCV infection and determining treatment outcome), and included genotyping (in the absence of a pan genotypic regimen). The cost of diagnostics and monitoring was estimated based, on pricing in developing countries. Thus, a “package” of HCV treatment and diagnostics could be available without genotyping for US $174 to $354; with genotyping, from US $264 to $444.\textsuperscript{57,68}
Figure 4. Minimum Cost for HCV Treatment, Diagnostics, Genotyping and Monitoring


5.2 Implementation

Using a public-health approach to HCV treatment—one regimen for everyone—will simplify procurement and delivery of treatment, especially if duration does not vary by genotype, subtype or cirrhosis. Some regimens do not require genotyping and subtyping, which are expensive and not always available.

The complexity and cost of HCV diagnostics are often cited as a barrier to treatment. Simplifying diagnostics by replacing anti-HCV and HCV RNA testing with a single antigen test; using a pan genotypic DAA regimen, and using another antigen test 12 or 24 weeks after treatment completion will radically simplify pretreatment assessment and minimize safety and efficacy monitoring.68

With DAAs, on-treatment efficacy monitoring is no longer necessary to determine HCV treatment outcome. Stopping rules for treatment failure are no longer relevant, since presence or absence of detectable HCV RNA at week 4 does not predict treatment outcome; end-of-treatment HCV RNA may not be reliable, since some people with detectable viremia may ultimately achieve SVR-12.69,70,71

HCV drug development has been done primarily by pharmaceutical companies, and driven by commercial interest. Companies have developed incestuous combinations instead of collaborating to identify optimal DAA regimens with best-in-class drugs. This approach has delayed development of, and access to promising regimens, and leaves many questions about DAA safety and efficacy in certain populations (although registries will provide additional information on DAA use and outcomes outside of clinical trials).

Some of the remaining questions include: need for ribavirin in certain populations; treatment safety and efficacy in understudied or excluded populations, clinical relevance of drug resistance, treatment sequencing, pharmacogenomics, and genotypes 5 and 6.

In HIV/AIDS research, information from trials run by pharmaceutical companies has been augmented—and optimized—by results from cohort studies, government-funded research networks, public-private partnerships and investigator-initiated trials. These trials often combine drugs from different companies, to assess HIV treatment strategies such as structured interruptions, simplification, or intensification in different populations. Generic drug producers were the first to combine antiretroviral agents from different pharmaceutical companies into fixed-dose combinations (FDCs) for resource-limited settings. Originator pharmaceutical companies eventually followed suit with Atripla, Complera/Eviplera, Evotaz and others.

In contrast, HCV drug development has been almost exclusively driven by the pharmaceutical industry. Companies have prioritized development of incestuous combinations rather than seeking to optimize regimens through collaboration. Commercial interests have prevented exploration of best-in-class DAA regimens, delayed access to promising regimens, and largely excluded people with common and serious comorbidities or urgent need for treatment from participation in registration trials. Thus, information on treatment safety, efficacy, tolerability and strategy comes from registration trials in carefully selected participants. Although some real-life data is becoming available from registries and small post-approval studies in high-income countries, regimens and strategies are the same as those used in clinical trials.
DAA mono therapy trials are short; for certain classes, regulatory agencies recommend limiting duration to three days, to forestall drug resistance.\textsuperscript{72} It is challenging to identify best-in-class drugs—or develop optimal regimens, since most regimens are comprised of drugs from one sponsor.

As the market for DAAs becomes saturated pharmaceutical companies will move from HCV into new areas, abandoning trials in key populations, and development and assessment of new treatment strategies or exploration of the relevance of pharmacogenomics.

6.1 Role of Ribavirin in DAA Regimens

The prevailing commercial strategies for DAA drug development are to shorten treatment, and remove ribavirin use. These may be at odds, since both longer treatment and ribavirin may be needed for people with the most advanced liver disease.

Although ribavirin has significant limitations (teratogenicity, and side effects including anemia; insomnia; irritability; anxiety; depression; insomnia; nausea; and muscle and joint pain), it is pan genotypic and it may bolster DAA treatment efficacy for certain regimens, genotypes and patient populations. In addition, it is no longer under patent protection and can be manufactured inexpensively.

In the DAA era, the role of ribavirin remains unclear. Although RBV use has not increased SVR in several phase II trials, the number of participants has been too small to determine if, and which patients will benefit from it. Indeed, ribavirin remains a mainstay of many trials in “harder-to-treat” populations (compensated and more advanced-stage cirrhosis, especially in genotype 3, and HIV/HCV).

In particular, RBV may be needed to cure genotype 3, especially in people with cirrhosis. In the ALLY-3 trial, 12 weeks of sofosbuvir and daclatasvir cured 96% of non-cirrhotic participants—but only 63% of cirrhotic participants.\textsuperscript{Error! Bookmark not defined.} In the ELECTRON-2 trial, adding RBV to 12 weeks of sofosbuvir/ledipasvir increased SVR from 64% to 100% among non-cirrhotic, treatment-naïve people with genotype 3; in treatment-experienced cirrhotics, sofosbuvir/ledipasvir plus RBV cured 73%\textsuperscript{73,74}.

6.2 Excluded and Under-Represented Populations: Pregnancy, Nursing, Paediatrics, Comorbidities, People Who Use and Inject Drugs, the Elderly

Despite the prevalence of HCV among women of childbearing age, there are not data on safety and efficacy of ribavirin-free DAA regimens during pregnancy and nursing. Information on safety of HCV treatment during pregnancy and nursing is particularly important, given that drug-drug interactions between DAAs and hormonal contraceptives may limit HCV treatment options or lead women to use less effective birth control during HCV treatment.
Paediatric trials (ages 3 to 17) of sofosbuvir and ribavirin and sofosbuvir/ledipasvir are underway. More research—especially of pan genotypic regimens—and optimal formulations are needed.

People 65 and over are often excluded from DAA clinical trials. To date, safety, efficacy and tolerability of DAAs in elderly patients—albeit without common comorbidities—do not differ from younger people. More research is needed.

Early stage or post-transplant DAA clinical trials often limit enrollment to people with mild liver disease (METAVIR SCORE F0 to F2). DAAs are likely to be more effective in people with mild liver damage; exploration of shortened treatment duration in this population is needed.

Although people with compensated cirrhosis are eligible for most DAA clinical trials, research in people with more advanced liver damage (Child Pugh stages B or C) is delayed until after approval. In the absence of compassionate use programmes (or those with limited eligibility), people with the most urgent need must wait until approval to gain access to potentially lifesaving DAAs in the absence of adequate safety and efficacy information.

HCV treatment is a priority for people with hepatic or renal impairment, and people with other significant, common comorbidities (including cardiovascular disease, type 2 diabetes, HBV coinfection, COPD, and depression). Typically, small, often single-dose pharmacokinetic (PK) studies are performed in people with renal or hepatic impairment before DAAs are approved, but actual trials do not occur until after approval. Often, people with other comorbidities are not eligible for clinical trials—and information on drug safety and efficacy in people with other illnesses does not emerge until drugs have been on the market for years.

Failure to include people who inject drugs, the highest-prevalence population, in clinical trials creates a vicious cycle, where treatment is withheld due to lack of evidence. After years of pressure from people who use and inject drugs and their advocates, people on opioid substitution treatment have not been completely excluded from clinical trials; a few HCV treatment trials are being conducted in active drug users.

### 6.3 DAAs and Pharmacogenomics

Researchers finally identified part of the reason for poorer response to interferon among African Americans: the IL-28B gene; this was only possible because of adequate representation in clinical trials. Some DAA regimens appear to be less effective in people with the IL28B TT genotype (most common among African Americans), especially when duration of treatment is shortened. With ombitasvir/paritaprevir/ritonavir and dasabuvir, ribavirin increased SVR in African Americans who had genotype 1a. Simeprevir dose may need to be adjusted in people of East Asian ancestry.
Other, unidentified pharmacogenomics factors may lessen or increase DAA treatment efficacy.

### 6.4 HCV Genotypes 5 and 6
DAAs are often characterized as pan genotypic, using data from in vitro studies. Safety and efficacy of HCV treatment across genotypes—and in people who are infected with multiple genotype (which occurs among people who inject drugs, dialysis recipients and others with multiple exposures to HCV) must be characterized in clinical trials.\(^{23,24}\) Data in genotypes 5 and 6 are limited. Although over a million people are infected with HCV genotype 5, only a handful them have been included in clinical trials of sofosbuvir-based regimens.\(^{21,77,78,79}\) Although DAAs have demonstrated efficacy in a small group of people with G5 or G6, more data are needed to inform regimen selection and global treatment scale-up.

### 6.5 HCV Drug Resistance and Treatment Sequencing
Mutations that confer resistance to one or more DAA classes may be present at baseline or after treatment failure. The prevalence of baseline resistance-associated variants (RAVs) varies by HCV genotype and subtype.\(^{80}\) For example, baseline RAVs associated with certain HCV protease inhibitors and non-nucleoside polymerase inhibitors have been observed in genotype 3a.\(^{81}\) In genotype 1, baseline NS5A RAVs have been found in 6% to 12%, although these do not always preclude successful treatment.\(^{80}\) In clinical trials of sofosbuvir/ledipasvir, prevalence of baseline NS5A RAVs ranged from 14% to 18%; although 90% of people with these baseline RAVs achieved SVR, post-treatment NS5A RAVs were found in most people who were not cured.\(^{33,82}\)

Sofosbuvir has a high resistance barrier. Although the S282T mutation has been selected in all genotypes during in vitro studies, the clinical significance of this RAV is unclear; it has been found in in 1 of 1545 trial participants, who was not cured.\(^{83}\) Other mutations have been associated with reduced efficacy and sofosbuvir treatment failure. The L159F mutation has been found at baseline and post-treatment in genotypes 1b and 3a; the V321A mutation has been detected after treatment failure in genotype 3a; C316N, and S282R may also reduce efficacy of sofosbuvir in genotype 1a.\(^{84,85}\)

The selection of first-line treatment will set the stage for a second-line regimen. Until the longevity and significance of DAA drug resistance is well understood, avoiding retreatment with DAAs from the same class—unless they have demonstrated sufficient activity against drug-resistant virus—is the preferred strategy. More information is needed on the relationship between baseline or post-treatment RAVs and HCV treatment—or retreatment outcomes.

Yet successful re-treatment with sofosbuvir may be possible, even for people who were not cured by a sofosbuvir-containing regimen. Lengthening treatment duration, adding ribavirin or use of additional DAAs may do the trick.\(^{43,86}\) In ELECTRON-2, 100% of 19 sofosbuvir-experienced participants were cured by retreatment with 12 weeks of sofosbuvir/ledipasvir
and ribavirin.\textsuperscript{73,74} Additional real-world experience is needed, to support recycling sofosbuvir.

For second-line regimens, the pan genotypic HCV protease inhibitors in late-stage development may prove essential for those who are not cured by an NS5A/nucleotide combination. Research of pan genotypic-based PI regimens must include people who were unsuccessfully treated with a nucleotide/NS5A regimen.

### 6. 6 Research Coordination and Opportunities

Scaling up global HCV treatment access is challenging, but offers the opportunity to leverage the lessons learned from HIV, where research has been invaluable. With HIV, prevention, treatment and testing programmes were established years before effective treatment was available. With HCV, we have the cure—but lack an independent research agenda for DAAs and their implementation. A coordinated plan to provide care and treatment while seeking to optimize it-- and assess the impact of doing so will make the most of resources.

DAAs offer an unprecedented opportunity: to nest a clinical research agenda within HCV prevention, testing, care and treatment programmes, and monitor outcomes. For example, screening initiatives could be used to validate diagnostic tools and provide surveillance data—which can be used to forecast treatment need, pool procurement, and allocate adequate resources, and inform the design and reach of prevention programmes. Treatment programs can embed questions on DAA safety and efficacy, explore ideal regimens and treatment duration through factorial trials, collect data on treatment outcomes and reinfection rates—and assess different models of care. Data from these programmes can be used to develop models to further inform resource needs and programmatic planning.

### 7. The HCV Treatment Pipeline

<table>
<thead>
<tr>
<th>By 2016, two fixed-dose combinations are likely to be approved. Both appear promising, but data are currently limited to results from small phase 2 trials.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some DAAs in the next batch will be pan genotypic, with activity against some of the mutations known to cause drug resistance. Sponsors are hoping to avoid ribavirin, and shorten treatment by combining DAAs from 3 classes.</td>
</tr>
<tr>
<td>By 2016, there will be additional HCV treatment options. Gilead and Merck have two-DAA FDCs in phase 3, and both companies are exploring triple DAA treatment.</td>
</tr>
</tbody>
</table>
7.1 Sofosbuvir-based FDCs

Gilead’s sofosbuvir/velpatasvir (NS5A inhibitor; formerly GS-5816) is a once-daily FDC in phase 3. Phase 2 results are promising, but more data are needed, especially in genotype 3 and cirrhosis, and genotypes 4, 5 and 6. In phase 2, after 12 weeks of treatment, SVR in genotype 1 ranged from 96% to 100%, regardless of ribavirin use, treatment history and cirrhosis; shortening treatment to 8 weeks—albeit in non-cirrhotic, treatment naïve study participants—did not appear to be a viable strategy for this regimen, even with ribavirin. In genotype 3, SVR in treatment-experienced, cirrhotic study participants was 88%; adding RBV to the mix increased SVR to 96%.87

The sofosbuvir/velpatasvir FDC is currently being studied in people who are treatment-naïve or treatment experienced (PEG-IFN and ribavirin, with or without an HCV protease inhibitor), in HCV genotypes 1, 2, 4, 5 and 6. The FDC is also being compared to 12 weeks (in G2) or 24 weeks (in G3) of sofosbuvir + RBV, and being studied in advanced liver disease: with or without ribavirin, in Child-Pugh Class B for 12 weeks, and for 24 weeks, without ribavirin, in Child-Pugh class C.

A phase 2 trial is assessing sofosbuvir, GS-5816 and GS-9857, a pan genotypic protease inhibitor in genotypes 1, 2, 3, 4, 5 and 6, treatment-naïve or –experienced people, with or without cirrhosis, for 6, 8 or 12 weeks.

Table 5. Sofosbuvir + GS-5816* With or Without RBV in Phase 279,87

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Duration</th>
<th>Treatment-experienced</th>
<th>Cirrhosis</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 weeks</td>
<td>NO</td>
<td>NO</td>
<td>81% + RBV (25/31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90% no RBV (26/29)</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>NO</td>
<td>NO</td>
<td>100% no RBV (28/28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100% no RBV (28/28)</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>YES</td>
<td>YES: Some participants were cirrhotic; data not broken out by cirrhosis status</td>
<td>96% + RBV (27/28) relapse occurred in a cirrhotic participant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100% no RBV (27/27)</td>
</tr>
<tr>
<td>2</td>
<td>8 weeks</td>
<td>NO</td>
<td>NO</td>
<td>88% no RBV (23/26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88% + RBV (23/26)</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>NO</td>
<td>NO</td>
<td>100% no RBV (10/10)</td>
</tr>
</tbody>
</table>

25
7.2 Grazoprevir/Elbasvir-Based Regimens

Merck’s grazoprevir/elbasvir FDC (formerly MK-5172, an HCV protease inhibitor, and MK-8742, an NS5A inhibitor) has entered phase 3. In the phase 2 C-WORTHY trial of grazoprevir/elbasvir, with or without ribavirin, cure rates in genotype 1 ranged from 93% (with RBV) to 98% (no RBV) in HCV monoinfection, and 87% (no RBV) to 97% (with RBV) in HIV/HCV.88

Grazoprevir and elbasvir also performed well in another genotype 1 trial, in treatment naïve people with cirrhosis, and treatment -experienced people with or without cirrhosis. An 8-arm trial compared 12 or 18 weeks of treatment, with or without RBV, in treatment-naïve people with cirrhosis, and treatment-experienced people (with and without cirrhosis). There were no significant differences in SVR by ribavirin use, subtype, cirrhosis, treatment duration or experience.89

Table 6. SVR among Cirrhotic Participants in C-WORTHY89

<table>
<thead>
<tr>
<th>Population</th>
<th>SVR, 12 weeks, + RBV</th>
<th>SVR, 12 weeks, no RBV</th>
<th>SVR, 18 weeks, + RBV</th>
<th>SVR, 18 weeks, no RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve, cirrhosis</td>
<td>90% (28/31)</td>
<td>(97%) 28/29</td>
<td>97% (31/32)</td>
<td>94% (29/31)</td>
</tr>
<tr>
<td>Treatment-experienced, cirrhosis</td>
<td>92% (23/25)</td>
<td>no significant difference for RBV vs. no RBV</td>
<td>100% (22/23)</td>
<td>no significant difference for RBV vs. no RBV</td>
</tr>
</tbody>
</table>

Merck’s FDC may become the backbone of an abbreviated, pan genotypic regimen. It is currently being studied in HCV genotypes 1, 2, 4, and 6, and in C-SWIFT, a phase 2 trial of the FDC and sofosbuvir, in genotypes 1 and 3. Interim data from C-SWIFT are available in genotype 1. Although the 4-week regimen yielded an SVR-4 of only 38% in non-cirrhotic
study participants, extending treatment to 6 weeks increased SVR-4 to 86% in non-cirrhotic participants (vs. 80% in cirrhotics); and 8 weeks of treatment cured 94% of cirrhotic participants.90

Merck is developing MK-3682, a nucleotide polymerase inhibitor and MK-8408, a pan genotypic NS5A inhibitor with activity against common NS5A RAVs.91 With these DAAAs, the company has the potential to construct pan genotypic, once daily regimens. They are studying MK-3682 with the grazoprevir/elbasvir FDC, and comparing efficacy of MK-8404 versus elbasvir with grazoprevir and MK-3682 in phase 2 trials.

8. Conclusion

*Perfectovir should not become the enemy of Goodovir.*

-Jennifer Cohn, Medical Director, MSF Access Campaign

Other promising DAA candidates are in early-phase development. With such high cure rates, improvements in DAA regimens are likely to be incremental and do not warrant delaying access until “perfectovir” appears—instead, the focus should be directed towards working with affected communities, scaling up and linking prevention and treatment programmes, building capacity among non-specialist providers to deliver these simplified regimens,92 The real challenge is no longer curing hepatitis C—it is getting treatment to the millions of people who need it, as soon as possible.

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