THE HEPATITIS C TREATMENT PIPELINE REPORT

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This report is dedicated to people everywhere who are fighting for access to HCV treatment, opioid substitution treatment, and access to injection equipment for themselves and their communities.

TAG

Treatment Action Group
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[E]fficacy data from randomized controlled therapeutic trials are commonly used to make important treatment decisions….This type of data is used widely by clinicians and patients to make the complex decision to embark on a long course of treatment that may be complicated by a variety of potentially significant side effects, may prove to be ineffective, and may be unnecessary. For these reasons, it is desirable for practitioners to know not only the efficacy of combination therapy as demonstrated in phase III registration trials, but also its effectiveness: the outcome of treatment in patients like their own receiving ordinary clinical care.

—Paul Feuerstadt et al. "Effectiveness of Hepatitis C Treatment with Pegylated Interferon and Ribavirin in Urban Minority Patients"

Introduction

Interferon is the therapeutic backbone of hepatitis C virus (HCV) treatment, as well as the major barrier to HCV treatment access, uptake, and completion. For many people, hepatitis C treatment does not work, and side effects can be debilitating. Fortunately, scientific advances and keen interest from the pharmaceutical industry have led to the development of dozens of new oral antiviral drugs for hepatitis C. Hopefully, it will soon be possible to replace interferon with a combination of HCV-specific oral drugs (commonly referred to as direct-acting antivirals, or DAAs) that will work for everyone.

Currently, two HCV treatment strategies are being evaluated: adding one or two DAAs to pegylated interferon and ribavirin (PEG-IFN/RBV), the current standard of care (SOC); and giving an all-oral DAA combination designed to inhibit different steps of the HCV life cycle (an approach that has been successful at controlling, but not curing, HIV infection). Adding a hepatitis C protease inhibitor to SOC has greatly improved response rates in phase II and phase III trials. Triple therapy (DAA plus SOC) may shorten treatment duration, depending on characteristics of the drug and the population it is used in. Drawbacks to triple therapy include more side effects, increased cost of treatment, and complex treatment algorithms that require frequent monitoring, and consideration of host, virus, and drug-specific characteristics.

The current SOC works by bolstering the immune response so that it can kill infected cells (immunologic effect), and protecting healthy cells by preventing HCV replication (antiviral effect). Oral antiviral agents can suppress HCV, but no one knows whether combination therapy with DAAs will render immune-based therapies such as peginterferon unnecessary; the answer will come from trials of interferon-free regimens. Results from the first of these trials are expected in 2012.

Although DAAs will change the HCV treatment paradigm, their effectiveness may be significantly limited by the emergence or development of drug resistance. In fact, HCV genetic mutations (polymorphisms) that render the virus resistant to one or more DAA classes have already been detected in people who have never used DAAs, and these mutations have also emerged during clinical trials—even when a DAA was used with peginterferon and ribavirin.

Background

Although it can be cured, HCV has been described by the World Health Organization (WHO) as a "viral time bomb" due to both its prevalence and its potential for causing serious, even life-threatening, complications. The WHO estimates that three percent of the world's population—or 170 million people—have been infected with hepatitis C; each year, 3–4 million more become infected (WHO 2010). Up to 130 million people have chronic hepatitis C, and at least 20% to 30% of them—or 26–39 million people—will develop cirrhosis if untreated or unsuccessfully treated. People with cirrhosis are at risk for liver cancer (hepatocellular carcinoma, or HCC) and liver failure; in fact, more than 365,000 people die each year from these HCV complications (Perz 2006).

In the United States, more than 3 million people have chronic hepatitis C, but at least half to three-quarters of them are undiagnosed, and the majority of those who have been diagnosed have not been treated (Armstrong 2006; Volk 2009). A survey of 280 people with HCV reported that 40% chose to defer HCV treatment due to fear of its side effects rather than to an inability to pay for it (Khokhar 2007). Even when HCV treatment is readily available and affordable, tolerability remains a problem. One study reported that only 1 of 56 veterans completed HCV treatment (Butt 2010).

Experts predict a sharp rise in HCV-related illness and death in the United States over the next two decades unless there are measurable improvements in HCV treatment efficacy, tolerability, access, and uptake (Davis 2010). Most people with HCV in the United States are over 50 years of age, likely to have been infected for decades, and thus especially vulnerable to developing cirrhosis and HCC (Armstrong 2006; Davila 2004; Davis 2010). Between 2001 and 2006, the Centers for Disease Control and Prevention (CDC) reported that the largest increase in incidence of HCC occurred among people 50–59 years of age (CDC 2010).

There is a very strong case for improving the efficacy, safety, and tolerability of, as well as access to, HCV treatment. Chronic HCV infection lowers productivity at work, increases health care use, and is associated with an increased risk for depression and liver-related morbidity and mortality (DiBonaventura 2010; McCombs 2010). A recent analysis of insurance claims data from over 17,000 people (HCV patients and an identical, uninfected group) reported that HCV infection significantly increases the risk of depression and serious clinical events. HCV doubles the risk of depression, increases the risk of HCC 25-fold, the risk of needing a liver transplantation more than 60-fold, and the risk of cirrhosis 80-fold (McCombs 2010).

Hepatitis C virus can be treated and—in some cases—cured (an outcome called sustained viralogical response, or SVR). HCV treatment is curative for only half of those who undergo it, and is less likely to work for the groups with the highest prevalence and most urgent need, such as African Americans, HIV/HCV-coinfected persons, transplant candidates and recipients, and people with cirrhosis.

SVR has been associated with significant decreases in liver-related morbidity and mortality, but the current standard of care is unlikely to have a significant impact on reducing domestic or global rates of HCV-related illness and death (Cardoso 2010; Morgan 2009; Singal 2010). HCV treatment access is limited by several factors beyond its constellation of side effects and exorbitant cost: doctors lack knowledge about, or interest in, treating their patients for hepatitis C; policy makers are apathetic about funding HCV care and treatment; reimbursement is inadequate; eligibility criteria are overly strict; and there are a host of medical contraindications (Volk 2009).

Access to HCV Treatment

In the United States, patent protection of peginterferon extends until 2016 (PegIntron) or 2017 (Pegasys), contributing to the high cost of treatment. In the United States, 48 weeks of treatment with peginterferon and generic ribavirin costs more than $30,000; this does not include physician and nursing time, laboratory monitoring, and additional medications.

In Europe, access to HCV treatment varies by country. At the beginning of 2005, France, Sweden, Germany, the Netherlands, and the Czech Republic had the highest treatment rates (>10% of prevalent cases); the lowest rates were found in Turkey, Romania, Poland, Greece, and Russia (<2% of prevalent cases) (Lettmeirer 2008).

The high cost and difficulty of administering peginterferon drastically limits access to HCV treatment: it is unavailable to most of the world's 130 million chronically infected people. According to *Viral Hepatitis: Global Policy*, a 2010 report from the World Hepatitis Alliance, more than 40% of the global population reside in countries that do not provide funding for HCV treatment, and over 80 percent of low-income countries would like assistance to increase treatment access (World Hepatitis Alliance 2010).

Lack of access to life-saving treatment for HCV is unacceptable. Pharmaceutical companies can remedy this situation. They have an opportunity to save millions of lives while generating unanticipated revenue and goodwill. Global access to peginterferon and DAAs can—and ought to be—facilitated by the following measures:

- Adopting a high-volume, low-profit strategy for low- and middle-income countries;
- Registering HCV treatments in all countries; and
- Granting voluntary licenses to generic manufacturers supplying low- and middle-income countries.

ABOUT BIOSIMILARS

Interferon is a biologic product. Biologics include vaccines and drugs made in tissue culture (living cells); interferon is a large complex protein manufactured in such cells. Generic versions of biologic products are called biosimilars, biogenerics, or follow-on biologics. Biosimilars have a different regulatory pathway from that for generic drugs.

Makers of generic drugs must demonstrate therapeutic equivalence (meaning that the active substances are identical) and bioequivalence (meaning that the drug is absorbed, distributed, metabolized, and eliminated within a similar range [80-125%] of the branded product); this means that formal, lengthy, and expensive clinical safety and efficacy studies are not required for generic drugs. Generic drug manufacturers do not have to pay for a full development program; this is one reason why their products are cheaper than their branded predecessors.

In contrast, biosimilar products must demonstrate similarity in quality, and in both clinical and nonclinical parameters, according to current guidance from the WHO and the European Medicines Agency (EMA). This means that biosimilar products need to undergo nonclinical and clinical studies, although a complete development program is not required.

In 2006, EMA issued its *Guideline on Similar Biological Medicinal Products*, and in October 2009, the WHO released its *Guidelines on Evaluation of Similar Biotherapeutic Products*. The United States Food and Drug Administration (FDA) is expected to issue guidance on biosimilar product development sometime after a November 2010 hearing. Hopefully, it will be possible to harmonize the regulatory pathway for biosimilars, so that safe, effective, and more affordable HCV treatment becomes globally available.

HCV Drug Development

The hepatitis C drug pipeline is robust. Many novel compounds and agents are undergoing extensive study, and a number of backup compounds are in preclinical development. In the coming years, the standard of care for HCV is likely to evolve rapidly and perhaps unexpectedly. Clinical uncertainty will be high as it is difficult to track a rapidly changing area of clinical management such as HCV infection.

Currently, drugs that inhibit different steps of the hepatitis C life cycle are in development; these prevent the virus from reproducing (the same principle used in HIV treatment). Therapies to stimulate the immune response to HCV, and drugs that inhibit hepatitis C via human host cell structures, such as entry inhibitors, are in clinical development. Several companies have more than one drug in development, and are working on in-house combinations, possibly co-formulated for convenient dosing—or for marketing advantage.

Following HCV drug development is difficult. New drugs are identified by letters and numbers rather than by names, and the field uses countless acronyms. Milestones for predicting response to, and evaluating efficacy of, new drugs continue to shift; and stopping rules for, and definitions of, nonresponse are also changing (see Box: Terms for HCV Milestones and Populations).

HCV trial design is complex and likely to become more so as the standard of care changes. Treatment strategy and duration are developed in accordance with the characteristics of the specific drug and the population under study, such as treatment-naive versus treatment-experienced, and subpopulations of treatment-experienced (such as null responders versus relapsers). With so many treatment permutations, it is difficult to get a clear picture of the effectiveness of these drugs across different populations.

Companies are often unwilling to disclose basic information (class, mechanism of action and structure, as well as study population) about candidates in early-phase trials because HCV drug development is fiercely competitive. Although HCV drug sales have been plummeting in the United States, they are expected to increase as new drugs enter the marketplace (from $2.3 billion to $4.5 billion by 2017). The United States ($1.9 billion), and the European Union ($1.7 billion) are expected to be the largest markets for new HCV drugs (Datamonitor 2009).

vRVR, RVR, eRVR, pEVR, and cEVR: predictors of HCV treatment outcome

vRVR: Very rapid virological response means that hepatitis C virus (called HCV RNA) cannot be detected in the blood after 14 days of treatment.

RVR: Rapid virological response means that HCV RNA cannot be detected in the blood after 4 weeks of treatment. RVR is a significant milestone in response-guided therapy (RGT; when duration of treatment is adjusted based on the response to treatment at week 4 and week 12).

> RVR predicts SVR in ~90% of cases—regardless of a person's HIV status—but the predictive value may change as the standard of care for HCV evolves (Jensen 2006; Martin-Carbonero 2008; Shea 2008; Yu ML 2008). RVR should not be the sole determinant of treatment duration; response after 12 weeks of treatment, IL-28B genotype, baseline HCV RNA, genotype and subtype, liver histology, and prior HCV treatment experience should also be considered. RVR should not be used as a stopping rule, because an SVR is still possible in the absence of an RVR.

> **Who Is Likely to Have an RVR?**
> Only 20% to 30% of people with HCV genotype 1 will have an RVR when treated with peginterferon and ribavirin (Dusheiko 2009; Jensen 2006). RVR is more likely for people with HCV genotype 1b and a low pretreatment viral load (≤400,000 to ≤600,000 IU/mL), and in people who receive an adequate ribavirin dose (Craxi 2009; Jensen 2006; Yu 2008); this group may only require 24 weeks of treatment with SOC, or SOC plus a DAA, to achieve SVR (Moreno 2010). Trials of peginterferon and ribavirin have reported SVR rates after 24 weeks ranging from 74% to 96% in people with genotype 1 and RVR (Ferenci 2008a; Yu 2008).

eRVR: Extended rapid virological response is a newly coined term for HCV RNA that is undetectable at week 4 and remains undetectable at week 12.

pEVR and cEVR: The response to HCV treatment at 12 weeks is crucial for predicting HCV treatment outcome. A complete early virological response (cEVR) means that HCV RNA is undetectable after 12 weeks of treatment. A partial early virological response (pEVR) means that HCV RNA has dropped by at least 2 logs (99%) after 12 weeks of treatment. People who have a cEVR are more likely to have an SVR than people who have a pEVR. An SVR is highly unlikely in the absence of pEVR or cEVR, so HCV treatment is usually discontinued at this point; this is often called a stopping rule.

EOT: End-of-treatment response means that HCV RNA is undetectable at the end of HCV treatment.

SVR-12: SVR-12 means that HCV remains undetectable (i.e., there is a sustained virological response) 12 weeks after completion of treatment. Although it has not been prospectively validated (meaning that researchers have found this to be true by looking back at trial results), SVR-12 is a good predictor of SVR because relapse usually occurs within a few weeks of treatment completion.

SVR: Sustained virological response means that HCV cannot be detected in the blood six months after completion of HCV treatment. SVR is long-lasting—regardless of HIV status—and associated with reductions in liver-related morbidity and mortality (Desmond 2006; Soriano 2004).

Relapse, breakthrough, nonresponse, and null response:
terms used to describe treatment-experienced populations, predict the
outcome of re-treatment, and determine the appropriate re-treatment strategy

Relapse occurs when HCV RNA reemerges after treatment, usually within weeks after completion. People who have relapsed after treatment with peginterferon and ribavirin are most likely to respond to re-treatment, particularly when a new agent is added.

Breakthrough means that HCV has reappeared during treatment after having been undetectable.

Nonresponse (also called partial response, or slow response) means that HCV has decreased by 2 logs (or 99%) at week 12, but does not become undetectable by week 24. Nonresponders to peginterferon and ribavirin are unlikely to achieve SVR when re-treated with the same regimen. Adding an oral antiviral may increase SVR, but nonresponders are at risk for developing resistance to a single oral antiviral. Vertex's PROVE 3, a phase II re-treatment trial in nonresponders, reported a 39% SVR when an HCV protease inhibitor was added to standard of care, versus 9% for standard of care alone (Manns 2009; McHutchison 2010a). Re-treating with more than one active antiviral agent may be the best strategy for prior nonresponders.

Null response means that HCV RNA has not decreased by at least 1 log (a factor of 10) after 4 weeks of treatment, or by 2 logs (99%) after 12 weeks of treatment. The dual definition is problematic, because some week-4 null responders do achieve pEVR after 12 weeks of treatment, although people with a drop of <0.5 log are more likely to remain null responders at week 12 (Picchio 2010). Null responders to peginterferon and ribavirin are extremely unlikely to achieve SVR when re-treated with the same regimen. In null responders, re-treatment with more than one oral agent should be explored, to lower the risk of drug resistance and increase SVR in this population.

Drug Resistance

Drug resistance is a significant limitation to DAAs. Drug resistance occurs when an organism—such as HCV—is able to grow or reproduce despite use of a drug that would normally stop it from doing so. HCV makes billions of copies of itself each day; they are not identical. Some individual virus particles (called virions) have structural changes in their genetic code (known as mutations); some mutations may confer drug resistance. Given HCV's high replication rate, the presence of mutations that cause resistance to one class—or multiple classes—of DAAs is not surprising.

Some mutations confer resistance to several, or all, of the agents within a class (this is called cross-resistance). Mutations at position A156 or R155 confer resistance to almost every hepatitis C protease inhibitor in clinical trials (Romano 2010).

Resistance to hepatitis C protease inhibitors has been detected after short-term monotherapy, and when an HCV protease inhibitor is used in combination with peginterferon and ribavirin (McHutchison 2009a; Sarazin 2007; Susser 2009a). The FDA now limits monotherapy studies of all antiviral drugs that have a low barrier to resistance to three days.

Preexisting resistance to DAAs (HCV protease inhibitors, HCV non-nucleoside polymerase inhibitors, and cyclosporine analogues) has been observed in people who have never used these drugs (Kuntzen 2008; Legrand-Abravanel 2009).

No one knows how long HCV resistance mutations will last, or if—and to what extent—they will compromise future hepatitis C treatment options. Unlike HIV, the hepatitis C virus does not integrate into the genome of host cells. Although researchers have discovered resistance mutations that have persisted for three to four years after monotherapy with hepatitis C protease inhibitors, a follow-up study of people treated with telaprevir (TP; an HCV protease inhibitor) plus SOC reported that 89% of unsuccessfully treated people did not have any resistant viral variants over a median of 25 months (range: 7–36) after discontinuing treatment (Forestier 2008; Susser 2009b; Zeuzem 2010c).

DAA resistance may pose a greater threat to HIV/HCV-coinfected people, who often have higher hepatitis C viral loads than HCV-monoinfected persons. Some experts have speculated that HIV treatment (with or without HIV protease inhibitors) may foster development of HCV mutations that confer resistance to hepatitis C protease inhibitors, possibly via immune reconstitution, but this remains controversial due to inconsistent findings (Blackard 2004; Morsica 2009; Winters 2010).

The clinical impact of HCV drug resistance remains unclear. Researchers and clinicians will need to know whether resistance mutations are present at baseline, the extent of resistance, and the relationship between degree of resistance and the drug efficacy, which may vary according to the concentration of individual drugs. A person who is somewhat resistant to hepatitis C protease inhibitors can still be treated successfully with one if it can be given at a high enough dose to overcome resistance, or if other drugs used in combination with it are effective enough to eradicate resistant virus. For example, a subset of participants with genotypes 2 and 3 experienced viral breakthrough after monotherapy with TP, but went on to achieve SVR after 24 weeks of peginterferon and ribavirin therapy (De Meyer 2010).

For now, HCV resistance testing is used only in research. Direct sequencing of HCV genetic material (RNA) can detect viruses that comprise at least 25% of the entire viral population. Other methods to detect and characterize HCV drug resistance are being explored by researchers for future use in clinical trials and clinical practice.

HCV Treatment Adherence

The new HCV antiviral agents require a far higher level of adherence than the current standard of care. With peginterferon and ribavirin, favorable HCV treatment outcomes are associated with adherence to at least 80% of the full dose of both peginterferon and ribavirin, for at least 80% of the treatment duration (known as the "80/80/80 rule") (McHutchison 2002). But the first generation of HCV antiviral drugs must be taken two or three times daily (BID and TID, respectively; i.e., at twelve - or eight-hour intervals) to maintain adequate drug levels. Unfortunately, more frequent dosing requirements are associated with poorer adherence (both as missed doses and incorrect intervals between doses) across different medical conditions (Claxton 2001; Greenberg 1990). Adherence education and support must therefore become an integral part of hepatitis C treatment.

Clinicians must be fully prepared to explain to their patients the importance of, and rationale for, adherence. Sponsors can help with adherence by co-formulating drugs, when possible, and through drug packaging, since blister packs can improve adherence (Huang 2000; Schneider 2008). Adherence support is particularly important for people with common comorbid conditions, such as HIV, type 2 diabetes, and depression, as they may already be on multiple medications with different dosing profiles and food requirements.

Some people are at higher risk for the emergence or development of drug resistance, such as HIV/HCV-coinfected persons (who typically have higher HCV RNA levels than people with HCV alone) and people for whom SOC is ineffective, such as prior non- and null responders (see Box: Terms for HCV Milestones and Populations). More data are needed to inform re-treatment strategies in these populations.

Strengthening the Backbone

Optimizing HCV treatment can lower the risk of drug resistance. Most research on optimizing HCV treatment has focused on ribavirin dosing and individualizing therapy according to viral response, HCV genotype, and other prognostic factors. Peginterferon alfa-2a (Pegasys) is prescribed more often than peginterferon alfa-2b (PegIntron) due to convenience—it does not require weight-based dosing. Most HCV clinical trials of new antiviral agents use Pegasys.

Pegasys may be more effective, as well as more convenient. Two head-to-head, randomized trials—both using weight-based ribavirin—compared Pegasys to PegIntron. Both reported that Pegasys was more effective than PegIntron, although their safety profiles were similar (Ascione 2010; Rumi 2010). In particular, Pegasys was significantly more effective than PegIntron for people with poor prognostic factors (HCV genotype 1, and HCV RNA >500,000 IU/mL) (Ascione 2010; Rumi 2010).

Further evidence for early efficacy of Pegasys versus PegIntron comes from the C208 study. This trial compared TP dosing (BID vs. TID) against a backbone of Pegasys or PegIntron (plus ribavirin). Duration of treatment was guided by response; people who had undetectable HCV RNA at week 4 and maintained it until week 20 stopped treatment after 24 weeks; those who did not meet these stopping rules were treated for a total of 48 weeks. Although response rates were similar across arms, people who were assigned to PegIntron were more likely to be assigned to 48 weeks of treatment than those in the Pegasys arms (Forns 2009; Marcellin 2009).

Predicting HCV Treatment Outcomes

The success of HCV treatment depends on a combination of drug characteristics, and host and viral factors (see Table 1. Predictors of Response to HCV Treatment with Peginterferon [PEG-IFN] and Ribavirin [RBV]). Successful HCV treatment must suppress the virus as quickly as possible—and keep it fully suppressed during treatment. But the speed and magnitude of the drop in hepatitis C viral load are only part of the story: drugs also need a high genetic barrier to forestall development of drug resistance. In addition, tolerability, pill burden, food requirements, dosing frequency, lack of drug-drug interactions, and metabolic pathway must be considered.

A New Tool for Predicting Response to HCV Treatment

Fortunately, years of research on identifying predictors of response to HCV treatment and ways to maximize response rates have paid off. Researchers have individualized HCV treatment by genotype, HIV status, early viral kinetics, and baseline HCV RNA. There are several known prognostic factors for response to HCV treatment with SOC, including race—African Americans are less likely than Caucasians to achieve SVR (see Table 1: Predictors of Response to HCV Treatment with Peginterferon [PEG-IFN] and Ribavirin [RBV]) (Conjeevaram 2006; Jeffers 2004; Muir 2004). Until recently,

researchers were unable to explain racial disparities between African Americans and Caucasians in both the likelihood of clearing HCV without treatment (called spontaneous viral clearance) and response to interferon-based treatment.

A recent discovery may help to predict HCV treatment outcomes with SOC, particularly for African Americans. Researchers have linked a polymorphism near the IL-28B gene with a greater probability of spontaneous viral clearance and interferon responsiveness in HCV-monoinfected and HIV/HCV-coinfected persons (Ge 2009; Rallon 2010; Thomas 2009). The CC genotype occurs most frequently among people of Asian ancestry, followed by those of European ancestry, and least often among persons of African ancestry. SVR is significantly more likely among African Americans with the CC genotype than among those with a TT or CT genotype (Ge 2009).

Patients, clinicians, and payers should not base HCV treatment decisions solely on IL-28B genotype. Other host factors, such as pretreatment levels of serum interferon–inducible protein-10 (IP-10), are predictive of response to peginterferon-based treatment on their own, and may augment the predictive value of IL-28B genotyping (Darling 2010; Diago 2006; Lagging 2006).

The relationship between the IL-28B CC genotype and responsiveness to HCV treatment without interferon is currently unknown.

Table 1. Predictors of Response to HCV Treatment with Peginterferon (PEG-IFN) and Ribavirin (RBV)

PRETREATMENT	ON TREATMENT
Genetics (IL-28b CC vs. CT or TT genotype)* Race/ethnicity (Asian >Caucasian >Latino/a >African American) (these may become less significant with the advent of interferon-free regimens)	Early response to treatment
HCV genotype (2, 3, 6, 4, 5, 1)** and subtype (1a vs. 1b)**	Weight-based ribavirin dosing
HCV RNA <400,000 IU/mL (this may become less significant with the advent of oral HCV antivirals)	Aggressive management of side effects
HIV status (not CD4 count or HIV RNA)	Adequate treatment duration
Liver damage/steatosis (these may become less significant with the advent of oral HCV antivirals)	Adherence (this will become increasingly important with the advent of oral HCV antivirals)
BMI	Support, education, and endurance
Insulin resistance/diabetes	Insulin resistance/diabetes
Age (this may become less significant with the advent of oral HCV antivirals)	N/A

*Recent discovery; has not been prospectively validated   ** Listed from most favorable to poorest prognostic factor

Diagnostics

Development of less expensive, more efficient hepatitis C diagnostic tests has often been overlooked in the quest for new treatments, despite its importance. Diagnosing hepatitis C is complicated and expensive, making follow-up difficult for many patients. A positive hepatitis C antibody test result requires confirmation by HCV RNA testing. Innovations such as antibody-antigen and dried blood spot testing will increase access to and reduce the cost of HCV diagnostics, particularly in nonclinical settings serving high-risk populations.

Antibody-antigen testing is more sensitive than antibody testing and less expensive than nucleic-acid testing. It may be useful for screening donated blood, streamlining HCV diagnosis, and identifying acute HCV (Ansaldi 2006; Tuke 2008). Detecting HCV in the acute phase (within six months after infection) is important, because treatment is far more likely to succeed in HCV-monoinfected and HIV/HCV-coinfected people when it is started during the period of acute infection (Vogel 2010; Weigand 2006). Antibody-antigen testing can shorten the diagnostic period for acute HCV by at least 20 days, and in more than 90% of cases it detected HCV infection among antibody-negative persons with detectable HCV RNA (Ansaldi 2006; La Perche 2005).

Dried blood spots from a single finger stick may replace separate tests for HCV antibody, RNA, and genotype. Using commercial assays, Tuaillon and colleagues performed genotyping, as well as antibody and viral-load testing, with the equivalent of three drops of frozen blood. Sensitivity and specificity of antibody testing with dried blood spots were almost 100%, and results of genotyping with dried blood spots were fully concordant with serum samples, while viral-load testing was less sensitive only when HCV RNA was <1000 IU/mL (Tuaillon 2010). Additional exploration and validation of dried blood spot testing are warranted.

HCV SUBTYPING ASSAYS

DAA resistance and viral breakthrough are more likely to occur with genotype 1a than genotype 1b (Kieffer 2007; Kukolj 2009; Lok 2010; Sarrazin 2007; Sarrazin 2010; Zeuzem 2010). Subtype may become more of a consideration in construction of HCV treatment regimens; thus, accurate subtyping is important, likely to become more so, and will require tests that sequence more than one part of the HCV genome. For example, a recent comparison of Versant's HCV genotype assay (LiPA) 1.0 (which looks at one region of the virus, the 5' UTR) versus LiPA 2.0 (which also looks at the core region) reported that addition of the core region results in significantly greater accuracy of genotyping and subtyping (Verbeeck 2008).

HCV RNA ASSAYS: STOP THE MADNESS!

Unfortunately, DAA clinical trials are currently using different HCV RNA assays; results have been reported as lower level of detection (LLoD) and lower level of quantification (LLoQ) or both. Different definitions of "undetectable" are being used to inform response-guided therapy, which creates confusion about appropriate stopping rules for each drug. In order to optimize treatment outcomes with DAAs, the field needs to arrive at consensus about standardizing assay use and reporting results consistently.

HCV Treatment and Population-Specific Issues

Response to HCV treatment varies widely in clinical trials versus clinical practice, and in different populations (see Table 2 and Figures 1-8. HCV Treatment Outcomes, by Population). Usually, the healthiest people are enrolled into clinical trials, representing a best-case scenario. Response rates to HCV treatment are usually much lower in clinical practice, where patients may have more advanced liver damage, other comorbid conditions, and additional poor prognostic factors than those eligible for clinical trials. New HCV treatments must be studied in clinically relevant populations with high HCV prevalence, poor prognostic factors, and urgent need for better HCV treatment. Priority populations include HIV/HCV-coinfected persons; African Americans; Latinos and Latinas; current and former injection drug users (IDUs); HCV treatment-experienced persons, especially those with cirrhosis; and transplant candidates and recipients.

If new antiviral drugs fail to cure HCV in treatment-experienced people, especially those with advanced liver damage, they may still suppress it. Long-term suppression of HCV may benefit people with advanced liver disease (Shiffman 2009), but long-term side effects of DAAs are unknown, and lifelong suppressive therapy is not an adequate solution for people with a curable disease. More effort must go into HCV drug development and research on treatment strategies so that a cure is available to the people who need it most, not just to those who are easiest to treat.

Table 2. HCV Treatment Outcomes, Clinical Trial and Clinical Practice, U.S. and Non-U.S.*

STUDY AND DATE	SOURCE	POPULATION	SVR
Fried et al.; *N Engl J Med* 2002; and *Manns et al.; Lancet* 2001	International clinical trial	HCV genotype 1	**42–44%** (Reference)
Feuerstadt et al.; *Hepatology* 2010	U.S. faculty practice vs. clinic practice	HCV genotype 1; 56% Latino/Latina, 27% African American, 9% Caucasian, 8% Other	14% Overall 27% Faculty practice 15% Clinic practice
Jacobson et al.; *Hepatology* 2007	U.S. clinical trial (community and academic setting)	HCV genotype 1; fixed-dose ribavirin vs. weight-based ribavirin	Fixed-dose RBV: 28.9% Overall 10.1% African American Weight-based RBV: 34% Overall 20.7% African American
Lee et al.; *Aliment Pharmacol Ther* 2006	Non-U.S. clinical practice (Canada)	HCV genotype 1; cirrhotic vs. non-cirrhotic	34% Cirrhotic 41% Non-cirrhotic

* Treatment with peginterferon plus ribavirin (weight-based or flat-dosing) for 24–72 weeks.

HIV/HCV Coinfection

Hepatitis C is a common and dangerous coinfection among HIV-positive people. Globally, an estimated 4-5 million HIV-positive people are coinfected with hepatitis C; approximately 25% of all HIV-positive people in the United States are coinfected with hepatitis C (Alter 2006). End-stage liver disease from hepatitis C coinfection is a leading cause of death among HIV-positive people in the United States and Western Europe, where antiretroviral therapy is widely available (Núñez-Fernández 2009; Weber 2006). The incidence of liver cancer among people with HIV has been increasing since 1995 (Daruich 2010). HIV coinfection more than triples the risk for cirrhosis, liver failure, and liver-related death from hepatitis C (Deng 2009). HCV progresses more rapidly in people with HIV, despite the use of antiretroviral therapy; significant fibrosis progression occurs in ~25% of coinfected people within three years (Bonnard 2007; Sulkowski 2007; Thein 2008).

HCV coinfection is associated with increased all-cause mortality among people with HIV, and a significantly greater prevalence of medical and psychiatric comorbidities (Backus 2005; Cachafeiro 2010; Chen 2009; Goulet 2005). HCV causes and worsens neurocognitive impairment among HIV-positive people (Hinkin 2008). Among HIV-positive people, coinfection with hepatitis C (particularly genotype 1) and advanced fibrosis are associated with markers of elevated risk for cardiovascular events (sICAM-1 and sVCAM-1) and all-cause mortality (IL-6 and d-dimer), as well as an increased risk of stroke (de Castro 2010; Kuller 2008; Peters 2010; Sico 2010).

Despite the prevalence and severity of HCV coinfection among HIV-positive people, coinfected people are less likely to be treated for HCV—and cured—than are people with HCV monoinfection (Butt 2009; Hall 2004; Mehta 2006). Poor prognostic factors, low response rates, high prevalence of medical and psychiatric comorbidities, and patient and provider reluctance are among the barriers to treatment access and uptake.

Figure 1. HCV Treatment Outcomes in HIV/HCV Coinfection (Genotype 1)

42–44% (reference SVR)

12
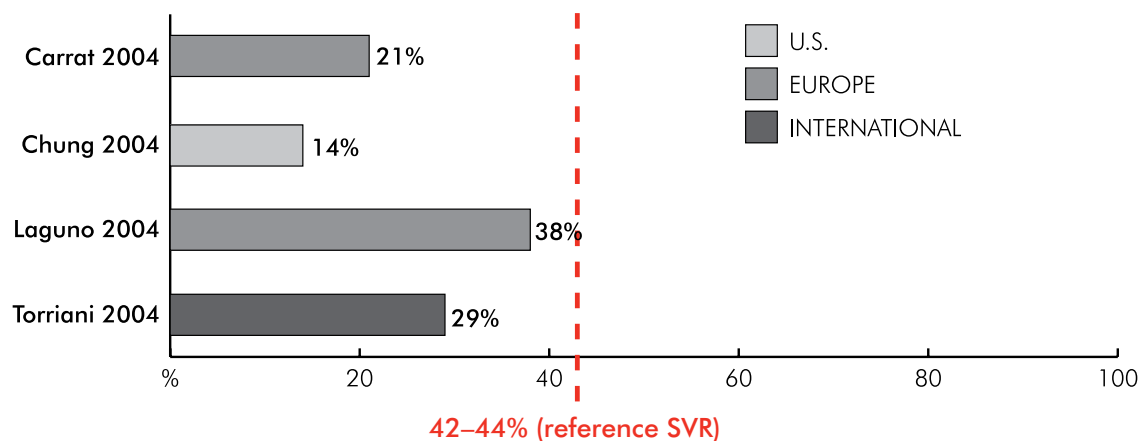
Drug-drug interactions between HIV antiretrovirals (ARVs) and HCV medications complicate treatment for coinfected people. Certain antiretroviral agents should be avoided during HCV treatment because their side effects can be exacerbated. For example, ribavirin and zidovudine (AZT; Retrovir) cause anemia, through different mechanisms (Moyle 2004; Reau 2008). AZT use during HCV treatment increases the incidence and severity of anemia, and leads to more HCV treatment discontinuations (Braü 2004; Mira 2007). Use of didanosine (ddI; Videx) with ribavirin is not recommended, because of a potentially life-threatening drug-drug interaction, and since concomitant didanosine and stavudine (d4T; Zerit) use during HCV treatment can worsen liver fibrosis (Bani-Sadr 2008; Moreno 2004). Efavirenz and interferon can cause neuropsychiatric side effects; coadministration may worsen these (Quereda 2008).

Drug-drug interactions between DAAs and ARVs are likely, as some share metabolic pathways (see Table 3. Known and Expected Drug-Drug Interactions between ARVs and Approved and Experimental HCV Drugs). Sponsors must perform drug-drug interaction studies promptly in order to facilitate preapproval trials in coinfected people, since most coinfected people will already be on treatment or within the CD4 threshold when antiretroviral therapy is recommended. Recent HIV treatment guidelines from the Department of Health and Human Services (DHHS) recommend HIV treatment initiation when the CD4 cell count is >350 cells/mm^3, and European AIDS Clinical Society (EACS) guidelines recommend that HIV/HCV-coinfected people initiate treatment when their CD4 cell count is between 350 and 500 cells/mm^3 (DHHS 2009; EACS 2009).

Given the rapid progression of, and high mortality from, HCV among HIV-positive people, drug-drug interaction studies should be performed as soon as dose and formulation allow so that lack of data does not delay initiation of HCV treatment trials in this population.

Table 3. Known and Expected Drug-Drug Interactions Between ARVs and Approved and Experimental HCV Drugs

ARVs	TELAPREVIR	BOCEPREVIR	RIBAVIRIN	PEG-IFN
PROTEASE INHIBITORS				
atazanavir/r	EXPECTED: b	EXPECTED: b	EXPECTED: a	NO
darunavir/r	EXPECTED	EXPECTED	NO	NO
fosamprenavir/r	EXPECTED	EXPECTED	NO	NO
indinavir	EXPECTED	EXPECTED	NO	NO
lopinavir/r	EXPECTED	EXPECTED	NO	NO
nelfinavir	EXPECTED	EXPECTED	NO	NO
ritonavir	EXPECTED	EXPECTED	NO	NO
saquinavir/r	EXPECTED	EXPECTED	NO	NO
tipranavir/r	EXPECTED	EXPECTED	NO	NO
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS				
efavirenz	EXPECTED	EXPECTED	NO	NO
etravirine	EXPECTED	EXPECTED	NO	NO
nevirapine	EXPECTED	EXPECTED	NO	NO
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS				
abacavir	NO	NO	EXPECTED: c	NO
didanosine	NO	NO	**YES**: d	NO
emtricitabine	NO	NO	NO	NO
lamivudine	NO	NO	NO	NO
stavudine	NO	NO	EXPECTED: d,e	NO
tenofovir	NO	NO	NO	NO
zidovudine	EXPECTED: g	EXPECTED: g	**YES**: f	NO
ENTRY INHIBITORS				
enfurvitide	NO	NO	NO	NO
maraviroc	EXPECTED: h	EXPECTED: h	NO	NO
INTERGRASE INHIBITOR				
raltegravir	NO	NO	NO	NO

Source: Seden K, Back D, Khoo S. New directly acting antivirals for hepatitis C: potential for interaction with antiretrovirals. *J Antimicrob Chemother*. 2010 Jun;65(6):1079-85. Used with permission.

YES: Interaction likely, do not use or use with caution.
EXPECTED: Potential interaction that may require close monitoring, dose or timing adjustment.
NO: No clinically significant interaction, or unlikely based on knowledge of drug metabolism.

a: hyperbilirubinemia
b: CYP3A4-mediated
c: guanosine analogue competition
d: mitochondrial toxicity
e: phosphorylation inhibition
f: hematological toxicity, anemia
g: overlapping toxicity, anemia
h: CYP3A4 competition

African Americans

In the United States, HCV is twice as prevalent among African Americans than among Caucasians (Armstrong 2006). New HCV treatments are important for African Americans, since interferon-based treatment is significantly less effective for African Americans than Caucasians due to a combination of host, viral, socioeconomic, and other factors (Donlin 2010; Ge 2009).

Enrollment of African Americans in registrational trials for HCV drugs has been inadequate to date; it hovers around 10-14% (Fried 2002; Kwo 2010; Manns 2001; McHutchison 2009a). However, postmarketing studies and other trials comparing HCV treatment safety, efficacy, and tolerability in African Americans versus Caucasians have demonstrated that African Americans do enroll in HCV clinical trials (McHutchison 2009b; Muir 2004). Safety, efficacy, and tolerability of new HCV drugs need to be characterized in African Americans, due to the high HCV prevalence and suboptimal treatment efficacy in this population.

Figure 2. HCV Treatment Outcomes, African Americans vs. Caucasians (Genotype 1)
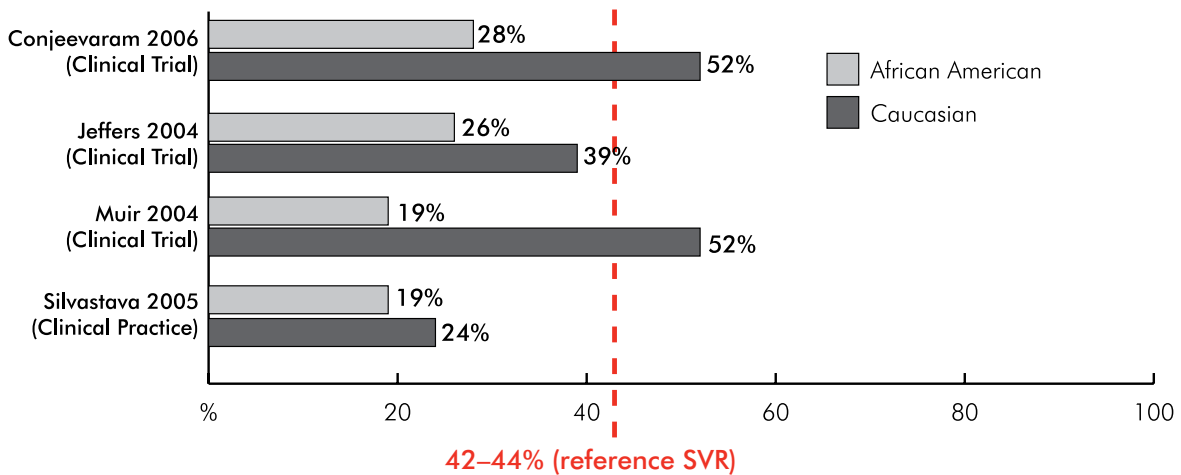
Latinos/Latinas

Despite genetic, geographic, and cultural heterogeneity among Latinos/Latinas, several studies have reported similar findings about the natural history of HCV in this population. The risk for, and prevalence of, serious liver damage from HCV is greater among Latinos and Latinas (versus Caucasians or African Americans) (Lepe 2006; Verma 2006). HCV treatment is also less effective for Latinos and Latinas versus Caucasians (Rodriguez-Torres 2009; Satapathy 2009). The aggressive nature of HCV and poor treatment outcomes warrant assessment of safety, efficacy, and tolerability of new HCV treatments in Latinos and Latinas.

Figure 3. HCV Treatment Outcomes, Latinos/as vs. Caucasians

Rodriguez-Torres 2009 (Genotype 1; Clinical Trial): Latino/a 34%, Caucasian 49%

Satapathy 2010 (Genotype 1; Clinical Practice): Latino/a 14%

Yu 2009 (Genotypes 2 & 3; Clinical Practice): Latino/a 67%, Caucasian 87%

Legend: Latino/a, Caucasian

42–44% (reference SVR)
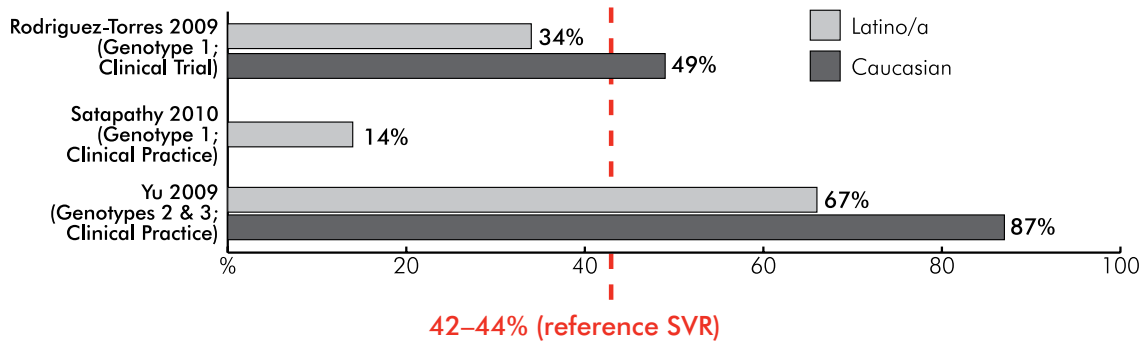
Figure 4. HCV Treatment Outcomes, Asian (Genotype 1)

Liu 2008 (Clinical Trial): 76%

42–44% (reference SVR)
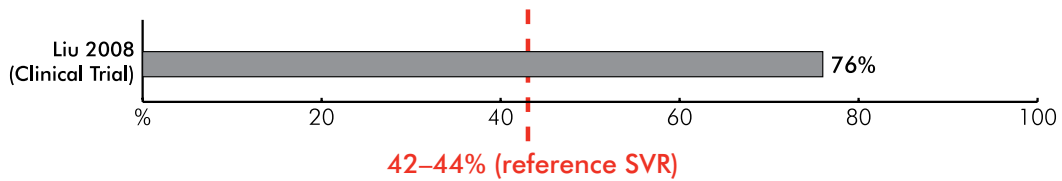
Current and Former Injection Drug Users (IDUs)

Although the predominant mode of HCV acquisition in the United States is injection drug use, people who currently use drugs are usually excluded from clinical trials unless they are maintained on methadone or buprenorphine. Clinical trials comparing SVR in IDUs versus non-IDUs have not reported significant differences between groups (Cournot 2004; Hellard 2009; Robaeys 2006). The exclusion of injection drug users from clinical trials perpetuates a vicious cycle: lack of clinical trials data on IDUs is perceived as a rationale for continuing to withhold HCV treatment from this highest-prevalence population, regardless of clinical indication for, and willingness to, undergo treatment.

Figure 5. HCV Treatment Outcomes, Injection Drug Users

Bruggmann 2008: 69%

Hellard 2009: 54% (Range 18-94%)

Legend: Clinical Practice, Meta Analysis

42–44% (reference SVR)
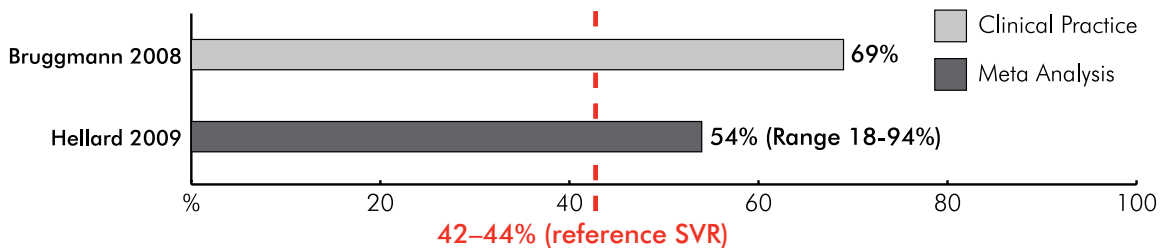
Non- and Null Responders

New hepatitis C treatment strategies are needed, particularly for non- and null responders. Although data are preliminary, adding an HCV protease inhibitor to standard of care has boosted response rates among some non- and null responders in phase III trials (Bacon 2010; Vertex press release, September 2010). More research on treatment strategies for non- and null responders to peginterferon is needed. Unfortunately, adding a single oral antiviral to standard of care may create a new category of treatment-experienced people with resistance to HCV antivirals. Re-treatment trials need to identify predictors of success, and optimal strategies.

Figure 6. HCV Treatment Outcomes by Prior Treatment Response
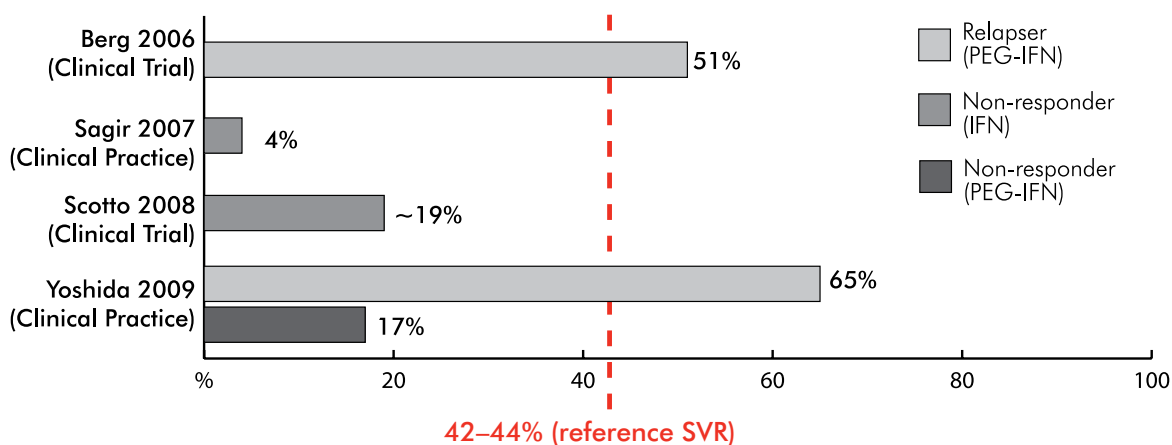
People with Cirrhosis

Experts estimate that 20% of newly diagnosed hepatitis C patients in the United States already have cirrhosis (Bell 2008). Although people with cirrhosis can be treated with peginterferon and ribivirin, adverse events are common, and treatment efficacy in people with cirrhosis is suboptimal, because disease severity is associated with impaired response to interferon-based treatment (Everson 2006). Nevertheless, successful treatment of HCV in people with cirrhosis significantly reduces liver-related illness and mortality (Morgan 2010). The high incidence of liver failure and liver cancer among people with hepatitis C–associated cirrhosis warrants efforts to enroll significant numbers of this population in preapproval studies.

Figure 7. HCV Treatment Outcomes, People with Cirrhosis
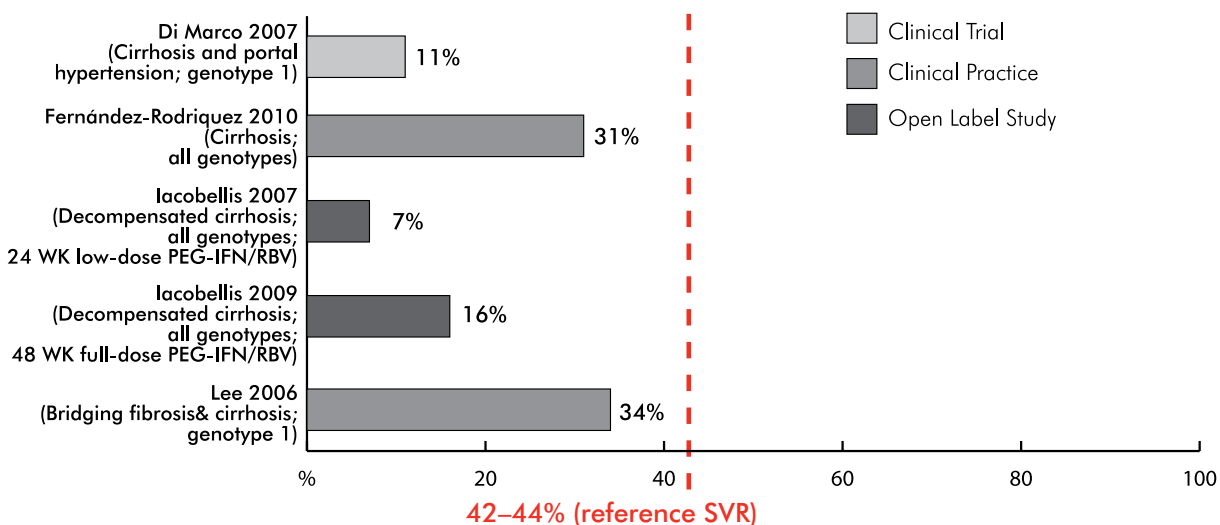
Unfortunately, people with compensated cirrhosis are usually excluded from, or underrepresented in phase II studies. It is difficult to assess SVR rates among people with cirrhosis, because peginterferon registration trials have aggregated SVR among people with bridging fibrosis and cirrhosis, instead of reporting them separately. One notable exception is Vertex's PROVE 3 trial, conducted in treatment-experienced people with HCV genotype 1. Although the overall number and percentage of study participants with cirrhosis was low (range: 11–20%), adding an HCV protease inhibitor to standard of care increased SVR in this group.

Table 4. PROVE 3: SVR in People with Cirrhosis

REGIMEN	OVERALL	CIRRHOSIS	NO CIRRHOSIS
TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12 weeks	51%	53%	51%
TP+PEG-IFN/RBV for 24 weeks, then PEG-IFN/RBV for 24 weeks	52%	45%	54%
TP+PEG-IFN for 24 weeks (no RBV)	23%	18%	25%
PEG-IFN/RBV for 48 weeks	14%	8%	15%

Source: Manns M, Muir A, Adda N, et al. Telaprevir in hepatitis C genotype 1-infected patients with prior non-response, viral breakthrough, or relapse to peginterferon-alfa 2a/b and ribavirin therapy: SVR results of the PROVE 3 study [abstract 1044]. 44th Annual Meeting of the European Association for the Study of the Liver. 22-26 April, 2009. Copenhagen, Denmark.

People with Hemophilia: A Case of Multiple Poor Prognostic Factors

Hepatitis C and HIV infections were virtually universal among people with hemophilia who used clotting factor concentrates before 1997. Since then, safer clotting factors and advances in HIV treatment have dramatically improved survival among people with hemophilia. Although HCV can be successfully treated in people with hemophilia, a cluster of poor prognostic factors limits its efficacy.

Many members of the aging cohort of people with hemophilia, hepatitis C, and HIV have already developed serious liver damage from HCV. A recent study reported bridging fibrosis or cirrhosis in close to one-fourth of HCV-monoinfected and HIV/HCV-coinfected adult males with hemophilia (Ragni 2010). Since aging, duration of HCV infection, and HIV coinfection are known accelerants of hepatitis C disease progression and poor prognostic factors for response to HCV treatment, safety and efficacy studies of DAAs should be prioritized in this population.

Transplant Candidates and Recipients

Ideally, new HCV treatments will obviate the need for liver transplantation. Until this is a reality, more effective and tolerable therapies are urgently needed for liver transplant candidates and recipients. In the United States and Europe, hepatitis C is the leading indication for liver transplantation. More than 35% of the 113,927 people listed for a liver transplant in the United States between 1985 and 2006 had HCV, versus 4.2% who had hepatitis B (Kim 2009). Of the 61,823 people who received liver transplants during the period between 1998 and 2007, 33% (20,305) had hepatitis C, versus 6% (3,820) who had hepatitis B (Mailey 2009). This disparity reflects the success of oral antiviral treatment for hepatitis B, versus the absence of safe and effective HCV treatment for people with advanced liver disease.

Hepatitis C almost always recurs after liver transplantation, and can progress rapidly, sometimes in a matter of months; cirrhosis usually develops within 8 to 10 years after transplantation (Gallegos-Orozco 2009; Terrault 2006). Researchers have tried different strategies, including preemptive treatment, to eradicate HCV prior to transplantation or immediately thereafter, versus waiting to initiate treatment until HCV recurs. The success of these approaches is limited by poor tolerability, adverse events, and risk of complications. In particular, interferon increases the risk of serious bacterial infections and hepatic decompensation among transplant candidates (Carrión 2009; Crippen 2002). However, if HCV can be suppressed prior to transplantation, reinfection of the new liver can be prevented, and successful HCV treatment after transplantation improves survival (Forns 2003; Picciotto 2007). We will not make a significant dent in HCV-associated pre- and posttransplant mortality until new, more effective, and safer HCV treatment is available.

Transplant candidates and recipients have the most to gain from HCV treatment, as well as the most to lose if drugs are not available through clinical trials or expanded/early access programs. Safety, efficacy, and tolerability of HCV antivirals should be studied in this population as soon as it is safely possible to do so.

Figure 8. HCV Treatment Outcomes, Transplant Recipients (Genotype 1)

42–44% (reference SVR)
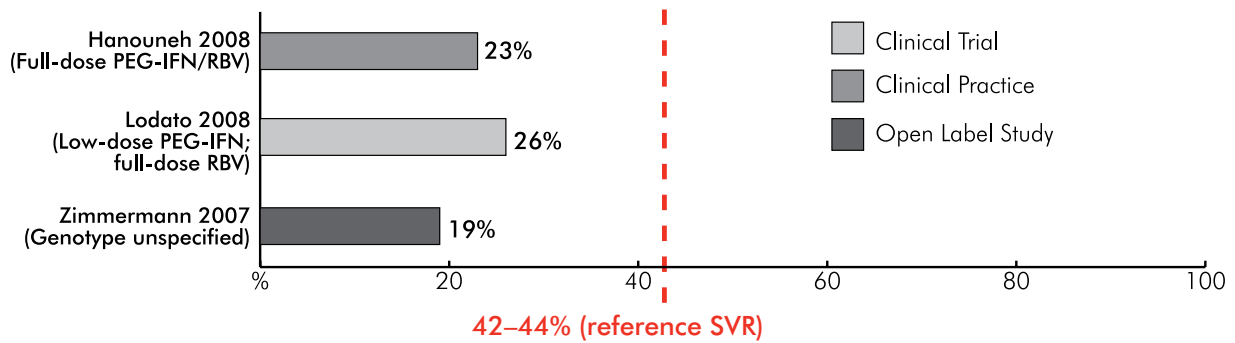
HCV Genotype and Subtype: Implications for Drug Development

Hepatitis C virus is highly variable: there are at least 6 HCV genotypes (numbered 1 to 6 in order of discovery), and each HCV genotype has more than 60 subtypes (lettered in order of discovery) (Kuiken 2008). Patterns of resistance differ according to HCV genotype, and even by subtype. For example, HCV protease inhibitors and non-nucleoside polymerase inhibitors are most effective against HCV genotype 1, but subtype 1a appears to be more resistance-prone than subtype 1b (Kieffer 2007; Kukolj 2009; Sarrazin 2007: Sarrazin 2010). In fact, viral breakthrough has been reported among people with HCV genotype 1a in two trials of DAA-only regimens (Lok 2010; Zeuzem 2010).

Mutations that confer resistance to HCV protease and non-nucleoside polymerase inhibitors have been detected in genotypes 2, 3, 4, and 5, especially in persons with high baseline HCV RNA (Dryer 2009; Kuntzen 2008; Legrand-Abravanel 2009; Le Pogam 2008; López-Labrador 2008).

HCV drug development follows both clinical need and market share. Most of the new HCV drugs were designed to work against HCV genotype 1, as it remains predominant in the United States and Western Europe (Fernández 1997; Maieron 2010; Martinot-Peignoux 1999; Nainan 2006; Roffi 1998). HCV will never be eradicated, however, until there are safe and effective drugs for all genotypes.

HCV drugs that are effective across genotypes, or that are designed to be active against specific, non-1 genotypes, must be developed. Infection with mixed genotypes has been documented in populations that are likely to have had multiple exposures to HCV, such as recipients of blood and blood products in the early-to-mid 1980s, and injection drug users (Preston 1995; Silva 2010). This may complicate treatment of these populations, since SOC is more effective against some HCV genotypes than others (see Table 5. SVR: HCV Genotypes 4, 5, and 6).

As immigration patterns change, and more people with genotype 1 are cured, the global distribution of HCV genotypes will continue to shift. For example, HCV genotype 4, which is predominant in the Middle East, is becoming more prevalent in France, Spain, Italy, and Greece, and HCV genotype 5 has spread from South Africa to Europe, North America, and Brazil (Antaki 2009; Bernier 1996; Cenci 2007; Delwaide 2005; Jover 2001; Levi 2002; Payan 2005). In Europe, HCV treatment uptake and outcomes have contributed to changes in the prevalence of HCV genotypes among HIV/HCV-coinfected people. Over the last decade, the prevalence of HCV genotype 3 has decreased among HIV/HCV-coinfected people in Europe, and genotypes 1 and 4 have become more prevalent (Medrano 2010; Ramos 2007).

Table 5. SVR: HCV Genotypes 4, 5, and 6

GENOTYPE	REGIMEN	SVR
HCV 4	PEG-IFN/RBV, varying duration	43–70%
HCV 5	IFN or PEG-IFN/RBV, varying duration	55–87%
HCV 6	PEG-IFN/RBV, 48 weeks	66–86%

Source: Antaki N, Craxi A, Kamal S, et al. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. *Liver Int.* 2010 Mar;30(3):342-55.

Unmet Need: HCV Prophylaxis

At present, there is no postexposure prophylactic strategy for hepatitis C. The rate of HCV transmission from occupational exposures ranges from 0.2% to 10% (Corey 2009). Clearly, research on the efficacy of oral antiviral agents for postexposure prophylaxis is warranted.

RVR IN THE CONTEXT OF NEW HCV TREATMENT STRATEGIES: THE NEW SVR?

Ideally, new HCV drugs and treatment strategies will boost RVR, ultimately leading to higher rates of SVR; but RVR does not always lead to SVR. Sponsors, investors, payers, clinicians, and people with hepatitis C are avidly following RVR rates, although SVR remains the most important outcome.

The Path Forward

It is unclear whether HCV will be cured without peginterferon, if an interferon-free cure is possible for all patient populations, and how many drugs will be required to cure HCV. For these reasons, it is crucial for pharmaceutical companies, researchers, regulators, and investors to look at the development of regimens as well as individual drugs so that the potential contribution of a drug to a regimen is considered, rather than its value in a drug-versus-drug paradigm alone. Though some drugs may fare poorly in head-to-head comparisons, they may be valuable components of a multi-drug regimen due to their side-effect profiles, activity against multiple genotypes or a particular subtype, lack of drug-drug interactions, dosing, and/or possibilities for co-formulation.

Speculation about the role of interferon will continue for the next couple of years, until safety and SVR data on all-oral antiviral regimens are available. For now, there is a snapshot from Roche's INFORM-1, a two-week proof-of-concept study combining an HCV protease inhibitor (RG7227) and an HCV polymerase inhibitor (RG7128) in treatment-naive and treatment-experienced people with HCV genotype 1.

INFORM-1 reported significant antiviral activity, especially in the highest-dose cohorts (see Table 6. INFORM-1: Activity of Protease/Polymerase Combination Therapy, at Highest Dose), without serious side effects or evidence of drug resistance (Gane 2009). However, in mid-November 2009, Roche announced that it was stopping the 900 mg dose of RG7227 in an ongoing phase IIb trial due to three cases of serious liver toxicity (grade 4; liver enzyme levels that are ten times the upper limit of normal); fortunately, these cases resolved after the drug was discontinued.

A dose-ranging study found that RG7227 could be used in combination with ritonavir, a pharmacokinetic booster that increases drug levels in the blood. Longer-term studies combining RG7128 and RG7227 are planned.

Achillion and Pharmasset have drugs from different classes in clinical development, but have yet to announce combination studies. Idenix Pharmaceuticals initiated a combination study of IDX 320 (an HCV protease inhibitor) and IDX 184 (a nucleotide polymerase inhibitor) that was stopped in September of 2010 due to liver toxicity. IDX 320 was thought to be the culprit and has been discontinued; development of IDX 184 will resume in mid-2011. In the meantime, groundbreaking multidrug studies are proceeding in parallel with trials adding a single drug to standard of care. Hopefully, these trials will provide proof of concept for interferon-free regimens.

Table 6. INFORM-1: Activity of Protease/Polymerase Combination Therapy, at Highest Dose

Cohort	Dose	Baseline HCV RNA (median)	HCV RNA: median change from baseline	HCV RNA below lower limit of quantification (<LLoQ; <43 IU/mL)	HCV RNA below lower limit of detection (<LLoD; <15 IU/mL)
Null responders, HCV genotype 1 N = 8	RG7128: 1000 mg BID RG7227: 900 mg BID	$6.5 \log_{10}$	$-4.9 \log_{10}$ (range: -3.5 to -5.3)	50% (4/8)	25% (2/8)
Treatment-naive, HCV genotype 1 N = 8	RG7128: 1000 mg BID RG7227: 900 mg BID	$6.5 \log_{10}$	$-5.1 \log_{10}$ (range: -3.0 to -5.9)	88% (7/8)	63% (5/8)

Source: Gane E, Roberts SK, Stedman CA, et al. Combination therapy with a nucleoside polymerase (R7128) and protease (R7227/ITMN-191) inhibitor in HCV: safety, pharmacokinetics, and virologic results from INFORM-1 [abstract 193]. 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2009). Boston, Massachusetts. 30 October-1 November 2009.

The first cross-company study, combining Pharmasset's nucleotide polymerase inhibitor, PSI-7977, with Bristol-Myers Squibb's NS5a inhibitor, BMS-790052, was announced in January 2011. The two drugs will be studied with or without ribavirin in treatment-naive people with HCV genotypes 1, 2, and 3. The study will be launched in the first half of 2011. Hopefully, this pioneering trial will set a precedent for other companies, so that people with HCV and their medical providers will have a greater range of information about the best possible therapeutic options.

Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, and Vertex have initiated studies combining two oral antiviral agents, with or without peginterferon and ribavirin. Early data are trickling in, but a more complete picture, including patient populations most likely to respond and predictors of response, will not be available until 2012.

Abbott is studying a triple-drug, peginterferon-free regimen in treatment-naive people with HCV genotype 1 and an IL28B CC genotype (see A New Tool for Predicting Response to HCV Treatment, page 8). This regimen combines: ABT-450/r, an HCV protease inhibitor boosted with ritonavir (used to increase drug levels, making them more effective, and lowering pill burden and dosing frequency); ABT-072, a non-nucleoside polymerase inhibitor; and ribavirin.

Bristol-Myers Squibb has launched a study in prior null responders with HCV genotype 1, combining BMS-650032, an HCV protease inhibitor, with BMS-790052, its first-in-class NS5A inhibitor. This landmark, open-label, three-arm study compares: 24 weeks of BMS-650032 plus BMS-790052 (dual therapy); 48 weeks of BMS-650032 plus BMS-790052; versus 24 weeks of BMS-650032 plus BMS-790052 with peginterferon and ribavirin (quad therapy).

In late 2010, results of a week-12 interim analysis were made public; this is the longest exposure to dual DAAs for which data are available. Although dual-DAA and quad therapy produced impressive decreases in HCV RNA at week 2 (median -5.1 to -5.3 $\log_{10}$), by week 12, quad therapy outperformed dual DDAs. In the quad arm, 90% (9/10) achieved cEVR at week 12 (vs. 45% [5/11] in the dual-DDA arm). All participants in the quad arm remained suppressed once they achieved undetectable HCV RNA, while 55% (6/11) of the dual-DAA arm—all with HCV genotype 1a and high baseline HCV RNA—experienced viral breakthrough, and resistance to both DAAs was detected. When peginterferon and ribavirin were added, 2 participants became undetectable, 2 had HCV RNA <25 IL/mL, and HCV RNA dropped by ≥1.5 $\log_{10}$ in the remaining 2. Of note, 9 of the 11 participants in the dual-DDA arm had genotype 1a, as did 9 of the 10 in the quad-therapy arm.

No serious adverse events, deaths, or treatment discontinuations have been reported, although three cases of neutropenia occurred in the quad arm; the peginterferon dose was reduced to manage these. The most common side effect was mild-to-moderate diarrhea (Lok 2010).

Boehringer Ingelheim has opened a two-part, peginterferon-sparing study exploring 24 or 48 weeks of BI 201335 (an HCV protease inhibitor given once daily) with BI 207127 (a non-nucleoside polymerase inhibitor; 400 or 600 mg, given TID) with or without ribavirin in treatment-naive people with HCV genotype 1.

Early data are promising, favoring the 600 mg dose of BI 207127 plus ribavirin; after 29 days of treatment, 100% (17/17) had HCV RNA <25 IU/mL (vs. 75% [11/15] for 400 mg plus ribavirin). The 400 mg dose was less effective for people with HCV genotype 1a than 1b, whereas the 600 mg dose was equally effective against 1a and 1b. A single viral breakthrough and one increase from nadir occurred in participants in the lower-dose arm; these patients were switched to peginterferon and ribavirin; and peginterferon, ribavirin, and BI 201355, respectively; both had a subsequent drop in HCV RNA (Zeuzem 2010a).

No treatment discontinuations or serious side effects were reported during the first four weeks of the study, though there were mild gastrointestinal events (nausea, diarrhea, and vomiting), rash, and photosensitivity. Although alanine aminotransferase (ALT; a liver enzyme) decreased, so did hemoglobin, and unconjugated bilirubin increased (Zeuzem 2010a).

Gilead has opened a response-guided study of quad therapy with GS 9256, an HCV protease inhibitor, in combination with GS 9190 (tegobuvir; a non-nucleoside polymerase inhibitor) plus SOC in treatment-naive people with HCV genotype 1. The design of this study was based on a three-arm study of 28 days of dual DAA (GS 9256 plus tegobuvir), with or without ribavirin, versus quad therapy (followed by SOC) in treatment-naive people with HCV genotype 1. Rapid virological response rates were significantly poorer in the dual-DAA arm (7%, or 1/15) and the dual DAA/ribavirin arm (38%, or 5/13) versus an RVR of 100% (14/14) in the quad arm. Dual- and triple-resistance mutations were seen during treatment except in the quad arm, where viral load was too low (<1000 IU/mL) to detect mutations. There was one discontinuation (for fatigue after addition of SOC). Although there were no grade 4 events, one person had a slight prolongation in QTc interval* and elevations in direct bilirubin developed in all four arms, indicating that one or both DAAs may be the culprit (Zeuzem 2010b).

Vertex's four-arm study of twice-daily dual-DAA therapy with telaprevir, an HCV protease inhibitor, and VX-222, an HCV polymerase inhibitor (followed by 24 weeks of SOC), versus quad therapy (for 12 weeks, followed by 24 weeks of SOC) is ongoing in treatment-naive people with HCV genotype 1. In October 2010, Vertex announced that it was discontinuing the 100 mg dose of VX-222 due to viral breakthrough, but the trial is continuing with the 400 mg dose of VX-222. Final results are expected in late 2011.

*a measurement of part of the heart rate; if prolonged, it can cause sudden death; in males, QTc >450 measured in seconds (ms) is abnormal; in females, QTc >470 ms; in this study, the QTc interval was 452 ms, but gender was not reported.

Characteristics of the Class: HCV Protease Inhibitors

Protease inhibitors have been used for more than a decade to treat HIV in combination with other antiretroviral drugs. Now, there are HCV-specific analogues of these drugs. Protease inhibitors block an important step in hepatitis C viral replication: cutting (or cleaving) of viral polyproteins (which are then reassembled into new virus particles). Protease inhibitors work in the same way that inserting something between the blades of a scissor prevents them from being able to cut.

HCV protease inhibitors will be the first class of DAAs available. Approval of the first generation, Merck/Schering Plough's boceprevir (BOC) and Vertex/Tibotec's telaprevir (TP) is expected in 2011, barring unforeseen circumstances. Although treatment strategies differ (see Table 8. Telaprevir and Boceprevir: Dueling Protease Inhibitors), adding one of these drugs to SOC has significantly boosted SVR among treatment-naive and treatment-experienced people with HCV genotype 1.

Resistance to a single HCV protease inhibitor—or to the entire class (called cross-resistance)—can develop or emerge within days. A mutation at position R155 confers resistance to seven of the HCV protease inhibitors currently in clinical trials (BI 201355, boceprevir, MK-7009, RG7227, telaprevir, and TMC 435350) (Sarrazin 2010). But HCV protease inhibitors active against common resistance mutations are in development, including Merck's MK-5172 (in phase I) and Achillion's preclinical candidate ACH-2684.

Regimens that include first-generation HCV protease inhibitors are likely to be complex, making adherence challenging. Boceprevir and telaprevir need to be taken three times a day (although a study comparing BID to TID dosing of telaprevir reported that efficacy was equivalent, and a phase IIIb study comparing BID to TID dosing is ongoing) (Marcellin 2009). Pill count ranges from 6 (telaprevir) to 12 (boceprevir) per day, not including ribavirin (which is taken twice daily).

Known side effects of HCV protease inhibitors include anemia, neutropenia, rash, anal itching and hemorrhoids, fatigue, nausea, vomiting, diarrhea, dysgeusia (bad or metallic taste in the mouth), headaches, dizziness, jaundice, and elevated alanine aminotransferase (ALT) and bilirubin.

Table 7. HCV Protease Inhibitors in Clinical Development

AGENT/SPONSOR	STATUS/POPULATION	COMMENTS
ABT-450 Abbott	Phase I/II; genotype 1, treatment-naive	Currently being studied with low-dose ritonavir plus SOC, and in combination with ABT-072, a non-nucleoside polymerase inhibitor
ACH-0141625 Achillion	Phase II; genotype 1, treatment-naive	Once-daily dosing
BI 201355 Boehringer Ingelheim	Phase II; genotype 1, treatment-naive and treatment-experienced	May be a once-daily drug; being studied as part of a peginterferon-sparing regimen in combination with BI 207127 (a non-nucleoside polymerase inhibitor), with or without ribavirin
BMS-650032 Bristol-Myers Squibb	Phase II; genotypes 1 & 4, treatment-naive	Genotype 4 and people with cirrhosis added in phase IIb; also being studied in combination with BMS-790052, an NS5A inhibitor, with or without SOC
Boceprevir Schering-Plough/Merck	Phase III; genotype 1, treatment-naive and treatment-experienced	TID (large pill burden: 12/day); anemia is a common side effect; limited data in null responders; likely to be approved in mid-2011
CTS-1027 Conatus	Phase II; genotype 1, null responders	24-week study with SOC
Danoprevir (formerly ITMN-191 and RG7227) Genentech/Roche	Phase I; genotype 1, treatment-naive Phase II; genotypes 1 & 4, treatment-naive (slated to open in mid-2011)	Has been studied with RG7128, a nucleoside polymerase inhibitor; dose-limiting liver toxicity was resolved with ritonavir boosting; is now being studied with and without ritonavir, plus SOC
GS 9256 Gilead Sciences	Phase II; genotype 1, treatment-naive	Being studied in combination with tegobuvir (GS 9190, a non-nucleoside HCV polymerase inhibitor) and SOC
GS 9451 Gilead Sciences	Phase II; genotype 1, treatment-naive	Once-daily dosing; being studied as part of quad therapy with tegobuvir (GS 9190, a non-nucleoside HCV polymerase inhibitor)
MK-5172 Merck	Phase I; genotypes 1 & 3 (males only)	Demonstrated activity against resistant virus in lab studies and chimps
Vaniprevir (MK-7009) Merck	Phase II; genotype 1, treatment-experienced	A phase II trial in treatment-naive people with HCV genotype 1 was withdrawn
Telaprevir Vertex/Tibotec	Phase III; genotypes 1, 2, 3, & 4, treatment-naive and treatment-experienced	Approval expected by mid-2011; also being studied with VX-222 (a non-nucleoside polymerase inhibitor), with or without SOC; twice daily dosing is being assessed in treatment-naive persons
TMC435350 Tibotec	Phase IIa; genotype 1, treatment-naive and treatment-experienced	Favorable dosing (possibly once daily); preliminary data suggests efficacy in treatment-experienced; two new capsule formulations being studied in healthy volunteers; Phase III studies in treatment naive and relaspers slated to open in early 2011
VX-985 Vertex	Phase I; genotype 1, treatment-naive	N/A

Boceprevir and Telaprevir: Leading Candidates

These two HCV protease inhibitors will be the first DAAs to market. Both are active against HCV genotype 1. Improvements in efficacy, dosing, and pill burden—and, hopefully, tolerability—are expected in coming years, when second-generation hepatitis C protease inhibitors will be available. The phase III boceprevir and telaprevir trials have moved the paradigm for DAA-based therapy to response-guided therapy (RGT), meaning that HCV treatment duration is based on early responses. Each drug has a unique treatment strategy. After a 4-week "lead-in" of peginterferon and ribivirin, BOC is added for 24 weeks, after which a 24-week peginterferon and ribavirin "tail" may be needed. TP is given with SOC for 12 weeks, followed by a 12- to 36-week peginterferon and ribavirin "tail."

Due to differences in study populations, stopping rules, treatment regimens and duration, side effects, and strategies used for their management, it is impossible to make a direct comparison of BOC to TP.

Table 8. Telaprevir and Boceprevir: Dueling Protease Inhibitors (results from phase II and phase III trials in treatment-naive people)

DRUG & STUDY	DOSING/PILL BURDEN	TREATMENT DURATION & STRATEGY	SVR	DRAWBACKS
Boceprevir **SPRINT-1**	TID 12 pills/day	**28 weeks** of triple therapy vs. 4-week lead-in with PEG-IFN/RBV, respectively	54–56%	Propensity to cause anemia; epoetin alfa used by the majority of people who had SVR
		48 weeks of triple therapy vs. 4-week lead-in with PEG-IFN/RBV, respectively	67–75%	Dysgeusia (bad or metallic taste in the mouth)
Boceprevir **SPRINT-2**	TID 12 pills/day	**28–48 weeks RGT:** 4-week lead-in with PEG-IFN/RBV; add BOC. If HCV RNA is undetectable at week 8 and week 24, stop treatment at week 28; if not, continue with 20 weeks of PEG-IFN/RBV.	67%; not broken out by duration of treatment, although 44% were eligible for shorter treatment	Results very difficult to interpret; complicated treatment algorithm creates large potential for errors in clinical practice. Duration of treatment varies according to response at weeks 8 and 24. Treatment paradigm is designed to optimize SVR in an easy-to-treat population.
Telaprevir **PROVE 1**	Q8 hrs* 6 pills/day	**24 weeks:** 12 weeks of triple therapy followed by 12 weeks of PEG-IFN/RBV.	61%	Rash—which can be severe—anemia, itchy skin, nausea, vomiting, and diarrhea

Telaprevir **ADVANCE**	Q8 hrs* 6 pills/day	**24-36 weeks RGT**: 8–12 weeks of triple therapy followed by 12 weeks (if eRVR) or 36 weeks (if no eRVR) of PEG-IFN/RBV.	75% for 12-week regimen; 69% for 8-week regimen (vs. 44% for control)	Rash—which can be severe—anemia, itchy skin, nausea, vomiting, and diarrhea
Telaprevir **ILLUMINATE**	Q8 hrs* 6 pills/day	**24-48 weeks RGT**: 12 weeks of triple therapy followed by 8 weeks of PEG-IFN/RBV; if HCV RNA is undetectable, 4 or 24 weeks of PEG-IFN/RBV; If detectable, 36 weeks of PEG-IFN/RBV	72% overall; for people with eRVR (undetectable HCV RNA at weeks 4, 12, and 20), SVR was 92% and 88% at 24 and 48 weeks, respectively. For people who did not have eRVR, SVR after 48 weeks was 64%.	Rash—which can be severe—anemia, itchy skin, nausea, vomiting, and diarrhea

*Every 8 hours; Q12hr TP dosing is being evaluated.

Sources:
Kwo P, Lawitz E, McCone C, et al. HCV SPRINT-1 final results: SVR 24 from a phase 2 study of boceprevir plus PegIFN alfa-2b/ribavirin in treatment naive subjects with genotype-1 chronic HCV [abstract 4]. 44th Annual Meeting of the European Association for the Study of the Liver. 22-26 April 2009. Copenhagen, Denmark.

McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med*. 2009;360:1827–1838.

For treatment-naive patients, BOC- and TP-based regimens offer the potential to shorten treatment duration from 48 weeks to 24–28 weeks. But HCV patients do not know the duration of their treatment in advance; it is not determined until 12–24 weeks after they have started it (see Table 9. Stopping Rules for Response-Guided Therapy with Boceprevir- and Telaprevir-Based Regimens). Telaprevir offers a clear advantage, since duration of treatment is determined at week 12. In contrast, the duration of a boceprevir-based regimen is not determined until week 24.

Table 9. Stopping Rules for Response-Guided Therapy with Boceprevir- and Telaprevir-Based Regimens

DRUG	WEEK 4	WEEK 8	WEEK 12	WEEK 24 ONWARD
Boceprevir	No stopping rule	No stopping rule	No stopping rule	If HCV RNA is detectable, stop all drugs. If HCV RNA is undetectable at weeks 8 and 24, stop treatment at week 28; If HCV RNA was detectable prior to week 24, add 20 weeks of PEG-IFN/RBV.
Telaprevir	If HCV RNA is >1000 IU/mL at week 4, stop TP, continue PEG-IFN/RBV.	No stopping rule	Stop TP; continue with 12 weeks of PEG-IFN/RBV. If no pEVR (<2 $\log_{10}$), stop all drugs.	If HCV RNA is detectable, stop all drugs.
PEG-IFN/RBV (single study data)	If HCV RNA is undetectable, stop treatment at 24 or 48 weeks.	If HCV RNA is undetectable, stop treatment at 36 or 48 weeks.	If HCV RNA is undetectable, stop treatment at 48 or 72 weeks.	N/A

Sources:
Jacobson IM, McHutchison JG, Dusheiko G, et al. ADVANCE Study Team. Telaprevir in combination with peginterferon alfa-2a and ribavirin in genotype 1 HCV treatment naive patients: final results of phase 3 ADVANCE study [abstract LB-2]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Poordad F, McCone J, Bacon BR, et al. SPRINT-2 Investigators. Boceprevir combined with peginterferon alfa-2b/ribavirin for treatment naive patients with HCV genotype 1: SPRINT-2 final results [abstract LB-4]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Sherman KE, Flamm SL, Afdhal NH, et al. ILLUMINATE Study Team. Telaprevir in combination with peginterferon alfa-2a and ribavirin for 24 or 48 weeks in treatment-naive genotype 1 HCV patients who achieved an extended rapid viral response: final results of phase 3 ILLUMINATE study [abstract LB-1]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Clearly, enhancing RVR with a DAA will push more people into SVR and shorten treatment duration. In SPRINT-2, people were given boceprevir after four weeks of standard of care, regardless of their response. This creates a quandary about how to use boceprevir. According to a recent study of RGT with peginterferon and ribavirin, people who have an RVR are unlikely to need a third drug to achieve SVR. In other words, people who have had an RVR are likely to achieve SVR without a DAA (Lee 2010).

Table 10. Results of Response-Guided Therapy with PEG-IFN/RBV

HCV RNA Undetectable	DURATION	SVR
Week 4	Treat for 24 or 48 weeks	84% for 24 or 48 weeks
Week 8	Treat for 36 or 48 weeks	73% for 36 weeks 74% for 48 weeks
Week 12	Treat for 48 or 72 weeks	49% for 48 weeks 40% for 72 weeks

Source:
Lee SS, Sherman M, Ramji A, et al. 36 versus 48 weeks of peginterferon alfa-2a plus ribavirin for genotype 1/4 patients patients with undetectable HCV RNA at week 8: final results of a randomized multicenter study [abstract 79]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

It is also not clear how to use boceprevir in people who have $<1\log_{10}$ drop in HCV RNA after the 4-week lead in. In SPRINT-2, poor response to the lead-in increased the risk for treatment failure and drug resistance. Boceprevir-based treatment led to SVR in only 29% of people with poor early response to SOC in the RGT arm (and 39% in the 48-week triple-therapy arm). Failure to respond to peginterferon and ribavirin increased the risk for resistance to boceprevir; it was detected in 47% of early poor responders in the RGT arm (and 35% of the 48-week triple-therapy arm) (Poordad 2010).

Because of its abbreviated treatment duration in treatment-naive people, as well as its simpler treatment algorithm, telaprevir may be the first choice for many physicians and their patients. Twice-daily dosing is being explored in a phase IIIb trial. The rash-management strategy has evolved, although this side effect may remain treatment-limiting for some people. To date, one case of drug rash with eosinophilia and systemic symptoms (DRESS) has been reported (Montaudié 2010).

Although effective, BOC has a complex treatment algorithm. Treatment-naive people will not know their duration of treatment until week 24, and most treatment-experienced people will require 48 weeks of treatment. Since people who are sensitive to interferon may not need BOC, and it is less effective for people with a poor early response to interferon, the population that BOC is most useful for is limited. Anemia is common side effect, usually treated with epoetin alfa, a red blood cell growth factor (see Box, Epoetin Alfa). A BOC treatment strategy trial, comparing ribavirin dose reduction versus use of epoetin alfa for management of anemia, is ongoing. BOC offers an important option for people who fear TP's side effects, or people who cannot tolerate TP.

Re-treatment with an HCV protease inhibitor added to SOC significantly increases SVR across all treatment-experienced populations. Most treatment-experienced people will require 48 weeks of treatment. Prior relapsers, since they are responsive to interferon, are most likely to be cured; SVR rates range from 68% to 88%. Nonresponders also benefit from adding an HCV protease inhibitor to SOC; SVR ranges from <40% to almost 60% in this group. Unfortunately, SVR among null responders hovers around 30% in TP trials (null responders were excluded from RESPOND-2). Data on response to boceprevir-based treatment in null responders are limited to results from RESPOND-1, a confusing phase II study, and extrapolation from studies in treatment-naive patients.

Table 11. Boceprevir and Telaprevir in Treatment-Experienced Populations

DRUG/STUDY & POPULATION	REGIMEN/STRATEGY	SVR	DRAWBACKS
Boceprevir Phase III **RESPOND-2** Prior relapse and nonresponse	4-week PEG-IFN/RBV lead-in, then RGT with BOC+PEG-IFN/RBV for 36 or 48 weeks	Overall: 59% Relapse: 68.6% Nonresponse: 40.4%	Serious adverse events more common in BOC arms (10–14% vs. 5% for SOC) Epoetin alfa was used by 41–46% of those in the BOC arms Most treatment-experienced patients will need 48 weeks of treatment
	4-week PEG-IFN/RBV lead-in, then BOC+PEG-IFN/RBV for 44 weeks	Overall: 66% Relapse: 74.8% Nonresponse: 51.7%	
	4-week PEG-IFN/RBV lead-in, then PEG-IFN/RBV+placebo for 44 weeks	Overall: 21% Relapse: 29.4% Nonresponse: 6.9%	
Telaprevir Phase II **PROVE 3** Prior relapse, breakthrough, and nonresponse	TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12 weeks	Overall: 51% Relapse: 69% Prior breakthrough: 57% Nonresponse: 39%	Treatment-experienced patients need 48 weeks of treatment. Higher discontinuation for adverse events in TP arms (15% pooled, vs. 4% for SOC); rash
	TP+PEG-IFN/RBV for 24 weeks, then PEG-IFN/RBV for 24 weeks	Overall: 53% Relapse: 76% Breakthrough: 62% Nonresponse: 38%	
	TP+PEG-IFN/RBV for 24 weeks	Overall: 24% Relapse: 42% Breakthrough: 36% Nonresponse: 11%	
	PEG-IFN/RBV+placebo for 48 weeks	Overall: 14% Relapse: 20% Breakthrough: 40% Nonresponse: 9%	
Telaprevir Phase III **REALIZE** Prior relapse, partial response, and null response	4-week PEG-IFN/RBV lead-in, then TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 32 weeks	Overall: 66% Relapse: 88% Partial response: 54% Null response: 33%	Only source of data is a press release; presentation expected in 2011
	TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 36 weeks	Overall: 64% Relapse: 83% Partial response: 59% Null response: 29%	
	PEG-IFN/RBV+placebo for 48 weeks	Overall 17% Relapse: 24% Partial response: 15% Null response: 5%	

Sources:
Bacon BR, Gordon SC, Lawitz E, et al. RESPOND-2 Investigators. HCV RESPOND-2: Final Results. High sustained viral responses among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when retreated with boceprevir plus PEGINTRON (peginterferon alfa-2b)/ribavirin [abstract 216]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

McHutchison J, Manns MP, Muir AJ, et al; PROVE 3 Study Team. Telaprevir for Previously Treated Chronic HCV Infection. *N Engl J Med.* 2010;362(14):1292-303 (a).

Adapted from Vertex Pharmaceuticals press release issued on 7 September 2010. Available at: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=505239 (accessed on 31 January 2011.)

Boceprevir in Treatment-Naive People

Instead of triple therapy—a "hit hard" approach successful for HIV treatment—Schering-Plough and Merck have used a four-week lead-in with standard of care in HCV SPRINT-1, their phase II study of treatment-naive people with HCV genotype 1, and all subsequent phase III trials. The lead-in is a treatment strategy intended to reduce the risk of resistance by lowering viral load before adding boceprevir. Experts have speculated that this strategy was developed to protect a weak drug. As a result, it is unclear how to best use boceprevir at either end of the early response spectrum. For example, boceprevir may not be necessary for people who have an RVR.

Lead-in is a useful screening strategy, since it identifies people who are not interferon-responsive (<1 $\log_{10}$ drop, or null response, at week 4), and avoids exposing them to virtual monotherapy with a DAA. Boceprevir has worked for a handful of fortunate early null responders. Kwo and colleagues reported that a small subset of treatment-naive people in HCV-SPRINT-1, a phase II trial, went on to achieve SVR with boceprevir, despite early null response (Kwo 2009a; Kwo 2009b). Since there are no predictors of SVR in early null responders, adding boceprevir in this situation is risky; a different treatment strategy, such as initiation of quad therapy, perhaps with a boosted protease inhibitor, is more likely to be effective.

SPRINT-1, a phase II trial in treatment-naive people, reported the highest SVR to date in HCV genotype 1: 75% in the 48-week lead-in arm (vs. 67% in the 48-week arm without a lead-in). In the shorter-duration arms, SVR was 56% in the lead-in arm (vs. 54% in the arm without a lead-in) after 28 weeks of treatment (Kwo 2010). Relapse rates in the shorter-course arms were higher, ranging from 24% (lead-in) to 30% (no lead-in); they dropped to 3% (lead-in) to 7% (no lead-in) with 48 weeks of treatment (vs. 24% for SOC) (Kwo 2009a). It is not clear whether the lead-in or the longer treatment duration bolstered response rates in this study.

The most problematic boceprevir side effect is anemia (defined as hemoglobin [HgB] <10 grams per deciliter [g/dL]). In HCV SPRINT-1, a phase II trial in treatment-naive people with HCV genotype 1, more than half of the participants treated with boceprevir developed anemia (vs. 34% of the control arm). In fact, most people in the boceprevir arms who achieved SVR used epoetin alfa (56-66% in the 24- to 28-week arms; 80-87% in the 48-week arms) (Kwo 2010).

EPOETIN ALFA

Epoetin alfa is a very expensive red blood cell growth factor. Safety of epoetin alfa is a concern, as are cost and access. Epoetin alfa carries a black box warning because it increases the risk of death or disease progression among cancer patients, and can increase the risk of stroke, heart attack, and heart failure in people with chronic kidney disease, although no warnings have been issued for its use during HCV treatment (FDA 2007).

Results from HCV SPRINT-2, Merck's phase III study in treatment-naive people with HCV genotype 1, are very difficult to interpret due to an elaborate study design and incomplete information; so far, data have not been published in a peer-reviewed journal (see Figure 9).

Figure 9. SPRINT 2: Boceprevir, Phase III (Treatment-Naive; N=1,097)

STUDY DESIGN

| | WK4 | WK8 | | WK24 | WK28 | WK48 |

RESPONSE GUIDED N=368

PEG-IFN/RBV | BOC+PEG-IFN/RBV

RGT: WK8 & WK24 HCV RNA

WK8 & WK24: UNDETECTABLE (44%): STOP TX @ WK28

WK8 DETECTABLE; WK24 UNDETECTABLE (22%): ADD 20WK PEG-IFN/RBV

TRIPLE N=366

PEG-IFN/RBV | BOC+PEG-IFN/RBV

CONTROL N=363

PEG-IFN/RBV | PLACEBO+PEG-IFN/RBV

TREATMENT DISCONTINUATION

RESPONSE-GUIDED

34%

9% - WK24 Detectable
12% - Adverse Events
13% - Other*

TRIPLE

37%

10% - WK24 Detectable
16% - Adverse Events
11% - Other*

CONTROL

55%

30% - WK24 Detectable
16% - Adverse Events
9% - Other*

* Causes for discontinuation not available

SVR RATES

- ■ RESPONSE-GUIDED
- ■ TRIPLE
- □ CONTROL

	OVERALL	NON-BLACK	BLACK
RESPONSE-GUIDED	63%	67%	42%
TRIPLE	66%	68%	53%
CONTROL	38%	40%	23%

Sources:
Bronowicki J, McCone J, Bacon BR, et al. Response-guided therapy (RGT) with boceprevir (BOC) + peginterferon alfa-2b/ribavirin (P/R) for treatment-naive patients with hepatitis C virus (HCV) genotype (G) 1 was similar to a 48-wk fixed-duration regimen with BOC + P/R in SPRINT-2 [abstract LB-15]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Poordad F, McCone J, Bacon BR, et al. SPRINT-2 Investigators. Boceprevir combined with peginterferon-2b/ribavirin for treatment naive patients with HCV genotype 1: SPRINT-2 final results [abstract LB-4]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Merck press release. 30 October 2010. Available at: http://www.merck.com/newsroom/news-release-archive/research-and-develop-ment/2010_1030.html (accessed on 1 February 2011).

The upshot of SPRINT-2 is that it enhances SVR in people who have an early response to peginterferon-based treatment: they are likely to achieve SVR after 28 weeks of treatment. Difficult-to-treat patients do not fare as well; they will require 48 weeks of treatment.

One cannot help but speculate that the confusion about SVR in the response-guided arm may be obscuring unfavorable information about boceprevir. Anemia remained problematic; more than 40% of participants in HCV SPRINT-2 used epoetin alfa. Dysgeusia was another common side effect, reported by more than 35% of participants who received boceprevir. The dropout rate for adverse events was 16% in both the control arm and the fixed-duration arm, and 12% in the RGT arm (Poordad 2010). There is no information on the number and timing of treatment discontinuations for reasons other than adverse events or treatment failure.

Boceprevir in Treatment-Experienced People

Results of RESPOND-1, the boceprevir phase II trial in non- and null responders, are very difficult to interpret due to significant changes in the protocol during the trial (adding ribavirin to all study arms and increasing boceprevir dose); the highest SVR rate was only 14% (Schiff 2008).

RESPOND-2 was a three-arm, 403-person study of boceprevir-based re-treatment in prior relapsers and nonresponders (null responders were excluded) with HCV genotype 1. RESPOND-2 also compared response-guided therapy to fixed-duration treatment.

It is clear that most treatment-experienced people will require 44 weeks of treatment with boceprevir-based regimens (see Figure 10). Many will also need epoetin alfa, since 44-46% of people in the boceprevir arms used it for a median range of 90-155 days (Bacon 2010).

Additional data on boceprevir in treatment-experienced people will be generated from PROVIDE, a single-arm study of people in the control arms of boceprevir trials who did not achieve SVR. Results are expected in 2013.

Figure 10. RESPOND 2: Boceprevir Phase III (Treatment-Experienced; N=403)

STUDY DESIGN

		WK4		WK8		WK36	WK48

LEAD-IN

RGT: WK8 HCV RNA

RESPONSE GUIDED (N=162)
PEG-IFN/RBV | BOC+PEG-IFN/RBV — WK8 UNDETECTABLE (46%): STOP TX @ WK36
BOC+PEG-IFN/RBV — WK8 DETECTABLE: STOP BOC @ WK36 | 12WK PEG-IFN/RBV "TAIL"

TRIPLE (N=161)
PEG-IFN/RBV | BOC+PEG-IFN/RBV

CONTROL (N=80)
PEG-IFN/RBV | PLACEBO+PEG-IFN/RBV

TREATMENT DISCONTINUATION

RESONSE-GUIDED

24%

8% - Adverse Events
16% - Other*

TRIPLE

16%

12% - Adverse Events
4% - Other*

CONTROL

55%

3% - Adverse Events
52% - Other*

* Causes for discontinuation not available

SVR RATES

Legend:
- RESPONSE-GUIDED
- TRIPLE
- CONTROL

OVERALL: 59%, 66%, 21%
PRIOR NON-RESPONDERS: 40%, 52%, 7%
PRIOR RELAPSERS: 68%, 75%, 29%

Sources:
Bacon BR, Gordon SC, Lawitz E, et al. RESPOND-2 investigators. HCV RESPOND-2: Final Results. High sustained viral responses among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when retreated with boceprevir plus PEGINTRON (peginterferon alfa-2b) ribavirin [abstract 216]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Merck press release. 30 October 2010. Available at: http://www.merck.com/newsroom/news-release-archive/research-and-development/2010_1030.html (accessed on 1 February 2011).

Telaprevir in Treatment-Naive People

Vertex's phase II studies, PROVE 1 (United States) and PROVE 2 (Europe and the United Kingdom) reported high SVR rates (61-69% after only 24 weeks of treatment) among treatment-naive people with HCV genotype 1 (see Table 8. Telaprevir and Boceprevir: Dueling Protease Inhibitors). PROVE 2 revealed the importance of ribavirin (demonstrated by higher rates of viral breakthrough and relapse, and a lower rate of SVR, in the ribavirin-sparing arm) (Hézode 2009; McHutchison 2009a).

In Study C208, Marcellin and colleagues explored response-guided therapy, BID versus TID dosing, and PegIntron versus Pegasys. The SVR rate was high, ranging from 81% to 85%, and the majority of participants (82%) required only 24 weeks of treatment because they achieved undetectable HCV RNA at week 4 and maintained it thereafter. Twice-daily dosing was equally effective, and there was no significant difference in SVR according to the brand of peginterferon (Marcellin 2009).

A pair of phase III studies, ILLUMINATE and ADVANCE, assessed response-guided treatment with telaprevir-based regimens in treatment-naive people with HCV genotype 1.

Figure 11. ILLUMINATE: Telaprevir Phase III (Treatment-Naive; N=540)

STUDY DESIGN

TREATMENT DISCONTINUATION

OVERALL	PRIOR TO WK20	WK20 - WK48
34%	19%	15%
7% - Virological Failure	2% - Virological Failure	4% - Virological Failure
18% - Adverse Events	11% - Adverse Events	7% - Adverse Events
9% - Other	5% - Other	4% - Other

SVR RATES
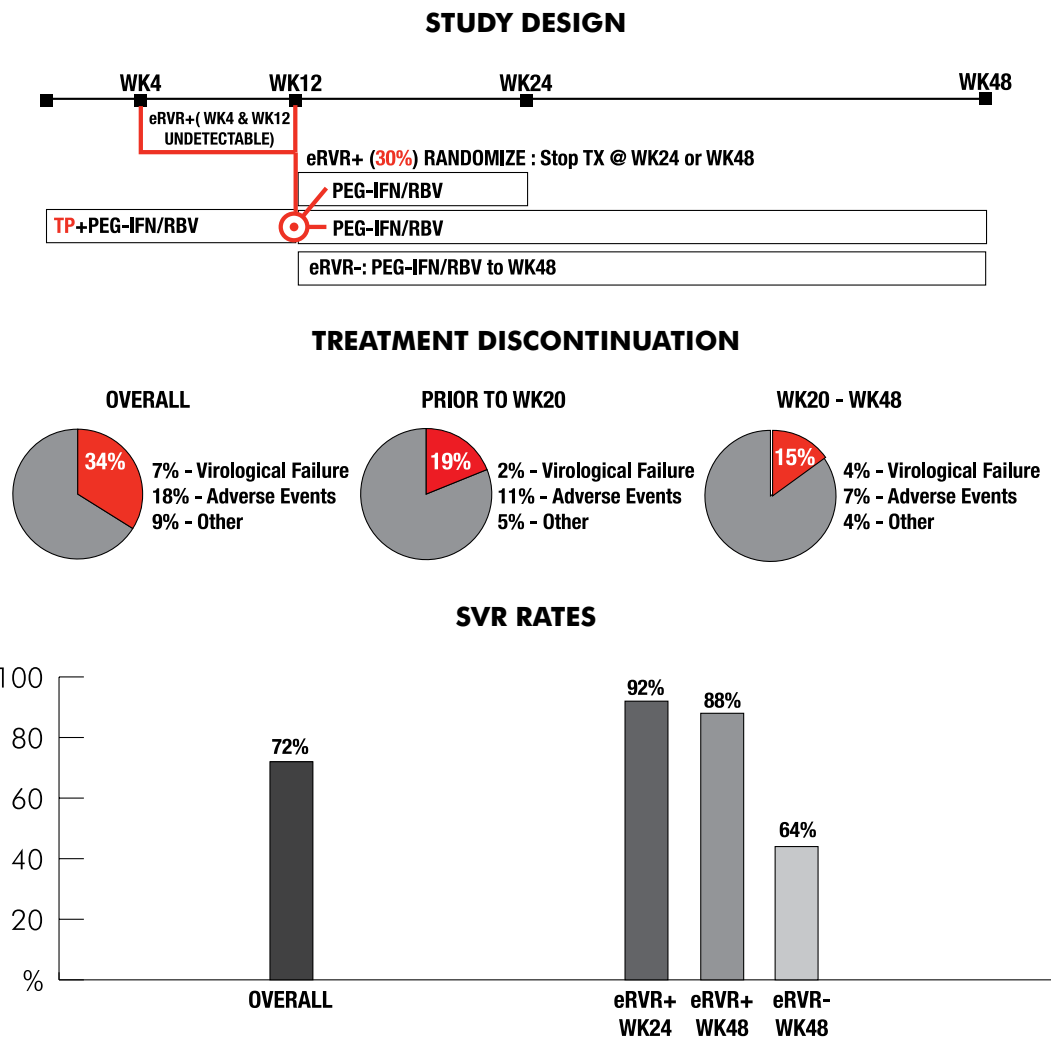
Relapse rates were low across all groups: 8% overall, and 6% for 24 weeks of treatment versus 3% for 48 weeks of treatment. Virtually all participants experienced at least one adverse event (99%), and 17% stopped all treatment due to adverse events (the most commonly reported were fatigue, pruritis, nausea, anemia, headache, and rash). Overall, 7% of study participants stopped telaprevir due to rash (the same percentage reported to have developed severe rash). Almost 40% of participants developed anemia, which was managed with ribavirin dose reduction; only 1% of participants discontinued due to anemia (Sherman 2010).

ADVANCE compared an initial 8 weeks of telaprevir plus SOC to 12 weeks of telaprevir plus SOC, followed by response-guided treatment with SOC (24-48 weeks, total).

Figure 12. ADVANCE: Telaprevir Phase III (Treatment-Naive; N=1,088)

STUDY DESIGN
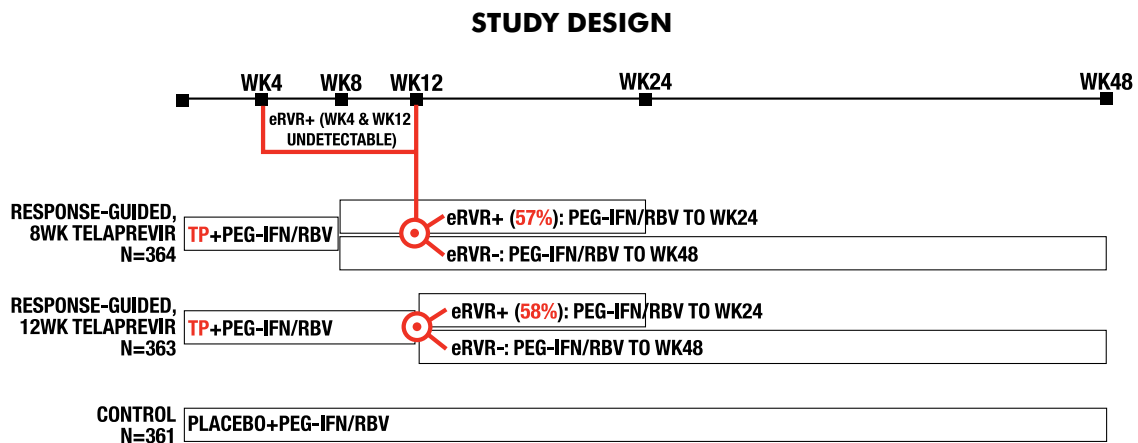
TREATMENT DISCONTINUATION
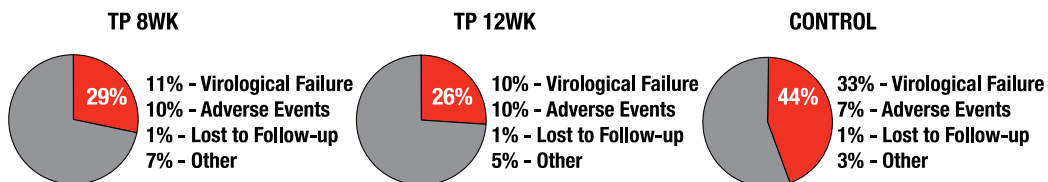
SVR RATES
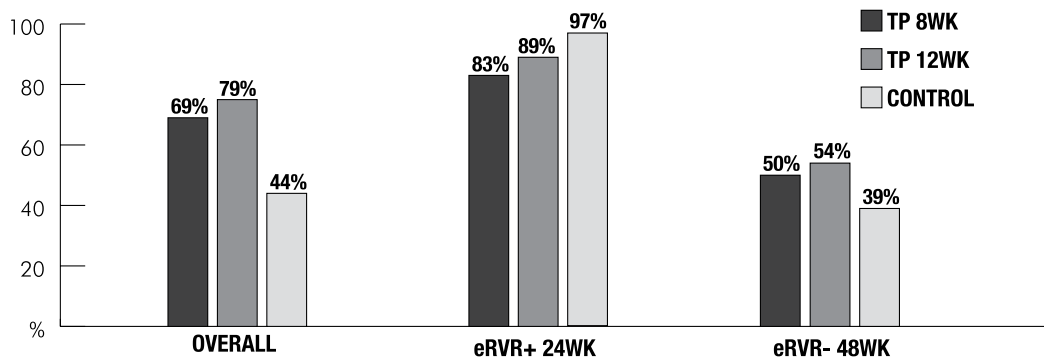
SVR rates were significantly higher in the telaprevir arms (69% to 75%) versus the control arm (44%). Almost 60% of participants who received telaprevir were eligible for shorter treatment (58% of the 12-week TP arm, and 57% of the 8-week TP arm, versus 8% of the control arm).

An extended rapid virological response (eRVR, meaning that HCV RNA is undetectable at week 4 and week 12) led to SVR in 89% (12-week TP) and 83% (8-week TP) of participants in the telaprevir arms (after 24 weeks of treatment). SVR rates were lower in people who did not have an eRVR (54% versus 50% in the 12-week and 8-week TP arms, and 39% in the control arm), although 97% of people with an eRVR in the control arm achieved SVR after 48 weeks of SOC.

Longer duration of telaprevir reduced virological breakthrough rates from 13% to 5%. Relapse rates were low (6% and 7%) in the TP arms versus the control arm (27%).

The most common adverse events, which were more frequent in the telaprevir arms, were pruritis, nausea, rash, anemia, and diarrhea. Severe rash was reported in 3% of the 8-week TP arm, 6% of the 12-week TP arm, and 1% of the control arm. Telaprevir (or placebo) was discontinued due to rash in 5% of the 8-week TP arm, 7% of the 12-week TP arm, and 1% of the control arm; less than 2% of participants in the TP arms discontinued all drugs due to rash. Anemia led 2% to stop TP, and 3% to stop all treatment, in the 8-week TP arm; in the 12-week TP arm, 4% stopped telaprevir, and 1% stopped all treatment; 1% of the control arm discontinued all drugs due to anemia. All told, 8% (8-week TP), 7% (12-week TP), and 4% (control) stopped all drugs due to adverse events during the first 8–12 weeks; 7% (8-week TP), 11% (12-week TP), and 1% (control) stopped telaprevir (or placebo) during the same period (Jacobson 2010).

Telaprevir in Treatment-Experienced People

Vertex has reported results from three studies in treatment-experienced people: PROVE 3, Study 107, and REALIZE (although REALIZE data are limited to those reported in a press release). Although SVR varied according to original pattern of nonresponse and duration of re-treatment, telaprevir has been effective in all subpopulations of treatment-experienced people. Unfortunately, it is less effective for people with the most urgent need: prior null responders.

Study 107 was a small trial made up of people previously enrolled in the control arm—meaning that they received SOC only—in prior telaprevir trials. All participants began the study with 12 weeks of triple therapy followed by SOC. The duration of re-treatment was 24–48 weeks. For null responders, the overall SVR was 37% (range: 17–56%, depending on duration of treatment). In partial responders, overall SVR was 55% (range: 0–100%). SVR was highest among people who had previously experienced viral breakthrough (75%; range: 0–86%) and relapse (97%; range: 96–100%) (Berg 2010).

In PROVE 3, Vertex studied the safety and efficacy of telaprevir-based regimens among treatment-experienced people (prior nonresponders, relapsers, and people who experienced viral breakthrough) (see Table 12. SVR from PROVE 3). Duration of treatment ranged from 24 to 48 weeks. Study participants were given either 12 or 24 weeks of triple therapy (unless randomized to the ribavirin-sparing arm). Longer treatment did not improve SVR among prior nonresponders, but did lower the relapse rate (13% vs. 30%). The importance of ribavirin was underscored by high relapse rates in the ribavirin-sparing arm (53%). Discontinuation rates were more than threefold higher in the telaprevir arms (15%) than in the control arm (4%); rash was the most common reason for discontinuation. As with Study 107, the highest SVR rates were among relapsers, and people who had experienced a previous viral breakthrough (Manns 2009; McHutchison 2010a).

Table 12. SVR From PROVE 3

REGIMEN	PRIOR RELAPSERS N=162	PRIOR NON-RESPONDERS N=260	PRIOR BREAKTHROUGH N=31	OVERALL (INTENT-TO-TREAT) N=453
TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12 weeks	69%	39%	57%	51%
TP+PEG-IFN/RBV for 24 weeks, then PEG-IFN/RBV for 24 weeks	76%	38%	62%	53%
TP+PEG-IFN (no RBV) for 24 weeks	42%	11%	36%	24%
PEG-IFN/RBV for 48 weeks	20%	9%	40%	14%

More telaprevir data in treatment-experienced people are expected in the second quarter of 2011, when results of REALIZE (a three-arm, 650-person study in treatment-experienced people with HCV genotype 1) are expected. In the meantime, Vertex issued a press release in September 2010 that included this table:

Table 13. SVR from REALIZE

REGIMEN	RELAPSERS N=354	PARTIAL RESPONDERS N=124	NULL RESPONDERS N=184	OVERALL (INTENT-TO-TREAT) N=662
Telaprevir arms (pooled)	86%	57%	31%	65%
4-week PEG-IFN/RBV lead-in, then TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 32 weeks	88%	54%	33%	66%
TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 36 weeks	83%	59%	29%	64%
PEG-IFN/RBV+placebo for 12 weeks, then PEG-IFN/RBV for 36 weeks	24%	15%	5%	17%

Source:
Adapted from Vertex Pharmaceuticals; press release issued on 7 September 2010. Available at: http://investor.shareholder.com/vrtx/re-leasedetail.cfm?releaseid=505239 (accessed on 1 February 2011).

Dropout rates in REALIZE were low: only 4% in the telaprevir arms (vs. 3% in the control arm) stopped treatment during the first 16 weeks; rash accounted for 0.4%, and anemia for 0.6%, of these discontinuations. Use of epoetin alfa was not permitted (Vertex press release. 7 September 2010).

HCV Protease Inhibitors in African Americans

Although enrollment of African Americans in all HCV protease inhibitor trials has been low (<15%), it is clear that adding an HCV protease inhibitor significantly increases cure rates among African Americans.

Table 14. Telaprevir and Boceprevir: SVR in African Americans

TRIAL & Treatment Strategy	TREATMENT ARMS	NUMBER OF AFRICAN AMERICAN PARTICIPANTS	SVR
ADVANCE RGT based on HCV RNA at week 4 & 12: If undetectable, stop at week 24; if detectable, continue PEG-IFN/RBV for 24 weeks (total 48 weeks)*	TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12 weeks, with or without 24-week PEG-IFN/RBV "tail"	**Total:** 8.6% (94/1088)	62% (16/26)
	TP+PEG-IFN/RBV for 8 weeks, then PEG-IFN/RBV for 16 weeks, with or without 24-week PEG-IFN/RBV "tail"		58% (23/40)
	PEG-IFN/RBV+placebo for 48 weeks		25% (7/28)
ILLUMINATE TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 8 weeks. RGT based on HCV RNA at week 4 & 12: If undetectable (eRVR+), randomized to a 4-week or 24-week PEG-IFN/RBV "tail" (total of 24 or 48 weeks of treatment); if detectable (eRVR-), continue PEG-IFN/RBV for 24 weeks (total 48 weeks)*	eRVR+: TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12 weeks (total 24 weeks)	**Total:** 14% (73/540)	88% (15/17)
	eRVR+: TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 36 weeks (total 48 weeks)		88% (15/17)
	eRVR-: TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 36 weeks (total 48 weeks)		35% (14/39)
PROVE 1	TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12-36 weeks	**Total:** 11% (27/250)	44% (8/18)
	PEG-IFN/RBV+placebo for 48 weeks		11% (1/9)
SPRINT-1 (Part 1 only)	4-week PEG-IFN/RBV lead-in, then BOC+PEG-IFN/RBV for 24 weeks	**Total:** 14% (78/520)	40% (7/18)
	BOC+PEG-IFN/RBV for 28 weeks		39% (6/15)
	4-week PEG-IFN/RBV lead-in, then BOC+PEG-IFN/RBV for 44 weeks.		53% (8/15)
	BOC+PEG-IFN/RBV for 48 weeks		29% (4/14)
	PEG-IFN/RBV for 48 weeks		13% (2/16)

SPRINT-2 4-week PEG-IFN/RBV lead-in, then BOC+PEG-IFN/RBV for 24 weeks. RGT based on HCV RNA at week 8 & 24: If undetectable - Stop at 28 weeks.If detectable - PEG-IFN/RBV for 20-week "tail"	BOC+PEG-IFN/RBV for 48 weeks	**Total:** 14% (159/1097) in a separate arm.	53% (29/55)
	BOC+PEG-IFN/RBV for 28 weeks, with or without PEG-IFN/RBV 20-week "tail"		42% (22/55)
	PEG-IFN/RBV+Placebo for 48 weeks		23% (12/52)

* If HCV RNA was >1000 IU/mL at week 4, TP was discontinued in arms A and B; if there was a <2 $\log_{10}$ drop at week 12, treatment was stopped, and if HCV RNA was detectable between week 24 and week 40, treatment was stopped.

Sources:
Jacobson IM, McHutchison JG, Dusheiko G, et al. ADVANCE Study Team. Telaprevir in combination with peginterferon alfa-2a and ribavirin in genotype 1 HCV treatment-naive patients: final results of phase 3 ADVANCE study [abstract LB-2]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2010;376:705–16.

McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med*. 2009;360:1827–1838.

Sherman KE, Flamm SL, Afdhal NH, et al. ILLUMINATE Study Team. Telaprevir in combination with peginterferon alfa-2a and ribavirin for 24 or 48 weeks in treatment-naive genotype 1 HCV patients who achieved an extended rapid viral response: final results of phase 3 ILLUMI-NATE study [abstract LB-1]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Note: Merck has not provided data on SVR among African Americans in RESPOND-2, a study of boceprevir-based therapy in prior relapsers and nonresponders. Approximately 12% of participants in RESPOND-2 were African American.

HCV Protease Inhibitors in Latinos and Latinas

Participants in SPRINT-2 and RESPOND-2 were broken out by geography and race (black vs. non-black), but not by ethnicity. Consequently, no data on SVR among Latinos and Latinas were presented; hopefully they will be included in upcoming publications (Bacon 2010; Poordad 2010).

In ADVANCE, ~10% of participants identified as Hispanic or Latino. SVR among Latinos and Latinas in the control arm was 39%. Adding 8 weeks of telaprevir in a response-guided regimen increased SVR to 66%, and SVR in the 12-week telaprevir arm was 74%. In ILLUMINATE, 67% of Hispanic/Latino participants achieved SVR overall; 94% in the 12-week telaprevir response-guided arm, and 82% of the group treated with 48 weeks of telaprevir-based therapy(Jacobson 2010; Sherman 2010).

HCV Protease Inhibitors in HIV/HCV-Coinfected People

Drug-drug interactions between HCV protease inhibitors and some antiretroviral agents may complicate treatment of hepatitis C in coinfected people. Nonetheless, small boceprevir and telaprevir trials in coinfected people are ongoing; results are expected in 2011 or 2012.

HCV Protease Inhibitors in People with Cirrhosis

Whether treatment-naive or treatment-experienced, people with cirrhosis have an urgent need for more effective HCV treatment to lower the risk of progression to liver cancer or liver failure; this population should be a priority for HCV drug development. Results are promising, but more DAA trials, particularly focusing on people with compensated cirrhosis, are needed.

Table 15. Boceprevir and Telaprevir in People with Cirrhosis (and Bridging Fibrosis) in Phase III Trials

TRIAL & Treatment Strategy	TREATMENT ARMS	NUMBER OF PARTICIPANTS with Cirrhosis	SVR
ADVANCE Phase III; treatment naive, RGT-based, 24–48 weeks	TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12 weeks, with or without 24-week PEG-IFN/RBV "tail"	22% (231/1088) F3 and F4 combined	62%
	TP+PEG-IFN/RBV for 8 weeks, then PEG-IFN/RBV for 16 weeks, with or without 24-week PEG-IFN/RBV "tail"		53%
	PEG-IFN/RBV+placebo for 48 weeks		33%
ILLUMINATE Phase III; treatment naive, RGT-based, 24–48 weeks	TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12 weeks (total 24 weeks)	27% (149/540) F3 and F4 combined	82%
	TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 36 weeks (total 48 weeks)		88%
RESPOND-2 Phase III; treatment-experienced, RGT (based on HCV RNA at week 8); 36–48 weeks	4-week PEG-IFN/RBV lead-in, then BOC+PEG-IFN/RBV for 32 weeks, with or without 12-week PEG-IFN/RBV "tail"	19% (77/403) F3 and F4 combined	SVR not reported by liver histology
SPRINT-2 Phase III; treatment-naive, RGT (based on HCV RNA at weeks 8 & 24); , 28–48 weeks	4-week PEG-IFN/RBV lead-in, then BOC+PEG-IFN/RBV for 24 weeks, with or without 20-week PEG-IFN/RBV "tail"	9% (98/1097) F3 and F4 combined	SVR not reported by liver histology

Sources:

Bacon BR, Gordon SC, Lawitz E, et al. RESPOND-2 Investigators. HCV RESPOND-2: Final Results. High sustained viral responses among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when retreated with boceprevir plus PEGINTRON (peginterferon alfa-2b)/ribavirin [abstract 216]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Jacobson IM, McHutchison JG, Dusheiko G, et al. ADVANCE Study Team. Telaprevir in combination with peginterferon alfa-2a and ribavirin in genotype 1 HCV treatment naive patients: final results of phase 3 ADVANCE study [abstract LB-2]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Poordad F, McCone J, Bacon BR, et al. SPRINT-2 Investigators. Boceprevir combined with peginterferon-2b/ribavirin for treatment naive patients with HCV genotype 1: SPRINT-2 final results [abstract LB-4]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October–2 November 2010.

Sherman KE, Flamm SL, Afdhal NH, et al. ILLUMINATE Study Team. Telaprevir in combination with peginterferon alfa-2a and ribavirin for 24 or 48 weeks in treatment-naive genotype 1 HCV patients who achieved an extended rapid viral response: final results of phase 3 ILLUMINATE study [abstract LB-1]. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October-2 November 2010.

Characteristics of the Class: NS5A Inhibitors

Researchers have not identified the function of the hepatitis C NS5A protein, but they know that it is essential for HCV replication. The first NS5A inhibitor, Bristol-Myers Squibb's BMS-790052, was discovered by scientists who screened a million different compounds in a laboratory for activity against hepatitis C virus, then eliminated candidates active against the HCV protease, polymerase, and helicase enzymes, finding a compound that inhibited a new target: the NS5A protein (Gao 2010; Murray 2010).

NS5A inhibitors may have cross-genotype activity, can be used in combination with DAAs from other classes, and are likely to be effective for people who have developed resistance to other DAA classes. Several candidates from this class are in preclinical and clinical development.

BMS-790052 demonstrated impressive potency after a single 100 mg dose. Longer-term data on this drug, although promising, are limited to 12 weeks. The side-effect profile of NS5A inhibitors is unclear so far, aside from reports of headache.

Table 16. NS5A Inhibitors in Clinical Development

AGENT/SPONSOR	STATUS	COMMENTS
AZD7295 Arrow Therapeutics/ AstraZeneca	Phase II	Future of this compound is uncertain, as sponsor is ceasing HCV drug development
BMS-790052 Bristol-Myers Squibb	Phase II; HCV genotypes 1 and 4, treatment-naive and treatment-experienced, and HCV genotypes 1, 2 and 3, treatment naive	Being studied in combination with Pharmasset's nucleotide polymerase inhibitor, PSI-7977 (with and without ribavirin) in HCV genotypes 1, 2 and 3, treatment naive Combination study underway in null responders combining BMS-790052 and BMS-650032 (protease inhibitor), with or without SOC; also studied in treatment-naive people with cirrhosis Study in HCV genotypes 1 and 4, treatment-naive, and nonresponders with HCV genotype 1
BMS-824393 Bristol-Myers Squibb	Phase II; HCV genotype 1, treatment-naive	N/A
CF102 Can-Fite	Phase I/II; HCV genotype 1	Also being studied as a treatment for liver cancer
GS 5885 Gilead Sciences	Phase I; HCV genotype 1, treatment-naive	N/A
PPI-461 Presidio	Phase Ib; HCV genotype 1, treatment-naive	Has pan-genotypic activity in lab testing; may be once-daily

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Characteristics of the Class: HCV Polymerase Inhibitors

Nucleoside, nucleotide, and non-nucleoside polymerase inhibitors have been part of combination HIV treatment for years. Now, HCV-specific analogues of these drugs are in development. Nucleoside and nucleotide polymerase inhibitors are imperfect copies of nucleotides that insert themselves into hepatitis C's RNA. Since they are faulty, other nucleotides cannot attach themselves; in other words, nucleoside and nucleotide polymerase inhibitors cause viral dead ends.

Some nucleoside/nucleotide polymerase inhibitors have already been discontinued for toxicity, but other candidates in this promising class are moving forward. If these are safe, effective, and tolerable, nucleoside/nucleotide polymerase inhibitors are likely to become the backbone of HCV treatment, since they are active across genotypes and have a high genetic barrier to resistance (meaning that resistance to this family of drugs is less likely to develop than resistance to protease inhibitors and non-nucleoside polymerase inhibitors).

Early results from trials of nucleoside and nucleotide polymerase inhibitors are promising, but these studies are small. Genentech—a subsidiary of Roche—is studying RG7128 or placebo plus SOC in treatment-naive people with HCV genotypes 1 and 4. After 8–12 weeks of SOC plus RG7128 (500 or 1000 mg BID), 68–87% of those who got active drug achieved undetectable HCV RNA, versus 49% of the placebo arm. No viral breakthrough occurred during treatment (Jensen 2010).

Non-nucleoside polymerase inhibitors interfere with HCV replication by binding to the hepatitis C polymerase and preventing viral replication—it's as if the virus is a car trying to park in a space that is now, due to drug binding, too small. The HCV polymerase enzyme has at least four binding sites, so it may be possible to combine non-nucleoside polymerase inhibitors that bind to different sites. So far, the hepatitis C non-nucleoside polymerase inhibitors in development are active only against HCV genotype 1, and resistance develops quickly. Mutations that confer resistance to non-nucleoside polymerase inhibitors have already been detected in people who have never taken these drugs (Dryer 2009).

Anadys's non-nucleoside polymerase inhibitor, ANA598, is being studied at two doses (200 or 400 mg TID) with SOC. After 12 weeks of triple therapy, participants continue with 12–36 weeks of SOC, depending on response. At week 12, 73% (19/26) of the 200 mg arm, and 75% (24/32) of the 400 mg arm achieved undetectable HCV RNA, versus 63% (19/30) of the placebo arm. Rash was a common side effect, particularly in the 400 mg arm. There was one discontinuation in the ANA598 arm due to treatment failure (Lawitz 2010).

Side effects reported in trials of nucleoside/tide and non-nucleoside polymerase inhibitors include nausea, vomiting, abdominal pain, flatulence, chills, headache, fatigue, myalgia, anemia, neutropenia, and rash.

Table 17. HCV Polymerase Inhibitors in Clinical Development

AGENT/SPONSOR	STATUS	COMMENTS
NON-NUCLEOSIDES		
ABT-333 Abbott	Phase I/II; HCV genotype 1; healthy volunteers and treatment-naive	N/A
ABT-072 Abbott	Phase I/II; HCV genotype 1; healthy volunteers and treatment-naive	Also being studied in combination with ABT-450/r, a boosted HCV protease inhibitor and ribavirin
ANA598 Anadys	Phase II; HCV genotype 1, treatment-naive	BID
BI 207127 Boehringer Ingelheim	Phase I; HCV genotype 1, treatment-naive and treatment-experienced	Being studied in combination with BI 201355 (an HCV protease inhibitor), with or without ribavirin
BMS-791325 Bristol-Myers Squibb	Phase II; HCV genotype 1, treatment-naive	N/A
Tegobuvir (GS 9190) Gilead Sciences	Phase II; HCV genotype 1, treatment-naive	Being studied with GS 9256, an HCV protease inhibitor and SOC Also being studied in combination with GS 9451, an HCV protease inhibitor, with SOC
IDX375 Idenix	Phase I; healthy volunteers	Possibly once- or twice-daily dosing
Filibuvir (PF-00868554) Pfizer	Phase II; HCV genotype 1, treatment-naive	N/A
VX-222 Vertex	Phase II; HCV genotype 1, treatment-naive	Also being studied in combination with telaprevir
VX-759 Vertex	Phase II; HCV genotype 1, treatment-naive	N/A
NUCLEOSIDES AND NUCLEOTIDES		
IDX184 (nucleotide) Idenix	Phase II; HCV genotype 1, treatment-naive	Clinical hold removed; phase II will be launched in mid-2011
INX-189 (nucleotide) Inhibitex	Phase I; healthy volunteers	Possibly once-daily dosing
PSI-7977 (nucleotide) Pharmasset	Phase IIb; HCV genotypes 1, 2, and 3, treatment-naive	Being studied in combination with BMS 790052, an NS5a inhibitor, with and without ribavirin Once-daily dosing; exploring 12 weeks of PSI-7997 plus ribavirin, with or without peginterferon for genotypes 2 and 3, treatment naive
PSI-352938 (nucleotide) Pharmasset	Phase I; HCV genotype 1	N/A

RG7128 (nucleoside) Roche/Genentech	Phase II; HCV genotypes 1 and 4, treatment-naive; also studied in nonresponders with HCV genotypes 2 and 3	BID
RG7348 (nucleoside) Roche/Genentech	Phase I; HCV genotype 1, treatment-naive	N/A
TMC 649128 (nucleoside) Medivir/Tibotec	Phase I; healthy volunteers	N/A

Characteristics of the Class: Cyclophilin Inhibitors

Cyclophilin inhibitors bind to cellular proteins that regulate the immune system. Some cyclophilin inhibitors have immunosuppressive activity. Both cyclophilin inhibitors in development for HCV (Debio 025 and SCY-635) bind to host cell proteins that may facilitate HCV replication, without immunosuppressive activity. Hyperbilirubinemia and low platelets have been reported in high-dose arms, but these resolved when Debio 025 was discontinued (Flisiak 2009).

Table 18. Cyclophilin Inhibitors in Development

AGENT/SPONSOR	STATUS	COMMENTS
Debio 025 Novartis	Phase IIb; HCV genotypes 1, 2, 3, and 4, treatment-naive and treatment-experienced	Also being studied as HIV treatment, and for HCV in HIV/HCV-coinfected people. Studied in HCV genotypes 2 and 3, treatment-naive people with ribavirin only, peginterferon only, and as monotherapy; and with SOC In treatment-experienced persons with HCV genotype 1
SCY-635 SYNEXIS	Phase IIa; HCV genotype 1, treatment-naive	People with IL28B T/T genotype excluded from this trial

Silibinin/Silymarin

Silibinin is extracted from the milk thistle plant; it is the active ingredient of silymarin. Milk thistle has been used for centuries to promote liver health; it is an antioxidant, an anti-inflammatory, and an antifibrotic.

Although the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial reported that silymarin had no antiviral effect against HCV, users had less nausea, appetite loss, and fatigue, and less liver, muscle, and joint pain, than nonusers did (Seeff 2008). In contrast, researchers have found that silymarin has antiviral activity against hepatitis C in the laboratory, including entry- and polymerase inhibition (Ahmed-Belkacem 2010; Wagoner 2010). Studies of intravenous silibinin in nonresponders found a dose-dependent effect on hepatitis C viral load, as did a study of oral silibinin in treatment-experienced persons with cirrhosis (Ferenci 2008b; Hawke 2010). There are two case

reports of SVR with silibinin; one in a treatment-experienced patient with cirrhosis, who achieved SVR after a ribavirin lead-in, followed by high-dose intravenous silibinin and SOC, and another in a liver transplant recipient, after 14 days of silibinin (Biermer 2009; Neumann 2010). Silibinin may be a promising therapy to prevent posttransplant HCV recurrence. Several trials are assessing safety and efficacy of oral and intravenous silibinin as treatments for hepatitis C.

Table 19. Silymarin Trials

AGENT/SPONSOR	STATUS	COMMENTS
Silibinin (intravenous) Medical University of Vienna	Phase II; all genotypes, nonresponders with SOC, or prior non-responders as monotherapy	Daily infusions for 21 days plus SOC; different infusion schedules for silibinin monotherapy
Legalon (capsules) National Center for Complementary and Alternative Medicine (NCCAM)	Phase II; treatment-experienced	TID for 24 weeks
Legalon (capsules) University of Maryland	Phase II/III; acute hepatitis C	TID for 4 weeks
Silymarin plus green tea extract (capsules) University of North Carolina–Chapel Hill	Phase I/II; all HCV genotypes, treatment-naive	Single site in North Carolina
Silymarin Buckwang Pharmaceuticals	Phase III; treatment experienced, HCV genotype not specified	Single site in Seoul, Korea
Silymarin (capsules) Mount Sinai School of Medicine	Phase I/II; HIV/HCV-coinfected	N/A

Other Antivirals in Development

Candidates with various additional types of potential antiviral activity are currently in clinical development.

Table 20. Antiviral Agents in Development

AGENT/SPONSOR	STATUS	COMMENTS
Clemizole hydrochloride Eiger BioPharmaceuticals	Phase I; HCV genotypes 1 and 2, treatment-naive	Anti-itching drug with activity against HCV
ITX 5061 iTherX	Phase I; HCV genotype 1, treatment-naive	Entry inhibitor
Serine C-palmitoyltransferase inhibitor (injection) Chugai/Roche/Genentech	Phase I	May inhibit HCV replication by interfering with HCV NS5A and lipid cell membranes
SPC3649 (injection) Santaris Pharma A/S	Phase I; healthy volunteers	Inhibits miR-122, a microRNA, to prevent HCV replication

Nitazoxanide (NTZ)

Nitazoxanide (Alinia) was approved in 2002 to treat diarrhea from two intestinal parasites (*Cryptosporidium parvum* and *Giardia lamblia*); since then, it has been studied for treatment of HCV genotypes 1 and 4 (see Table 21. NTZ and SVR). Currently, nitazoxanide monotherapy is being studied to prevent posttransplant HCV recurrence, and in combination with SOC in treatment-naive and treatment-experienced HIV/HCV-coinfected people who have genotype 1. In Egypt, nitazoxanide plus SOC is being studied in people with HCV genotype 4.

Table 21. NTZ and SVR

STUDY	POPULATION	SVR	COMMENTS
STEALTH C-1 12 weeks of NTZ, followed by 36 weeks of SOC; or 12 weeks of NTZ, followed by 36 weeks of PEG-IFN; vs. SOC	HCV genotype 4	61% (NTZ + PEG-IFN) 79% (NTZ + SOC) 50% (SOC)	In genotype 4, SVR ranges from 43% to 70% with SOC
STEALTH C-2 4 weeks of NTZ or placebo, followed by 48 weeks of triple therapy (NTZ + SOC or placebo)	HCV genotype 1, 80% null- and nonresponders	7% (NTZ + SOC) 0% (SOC + placebo)	Missing data on response to prior treatment in 20%
STEALTH C-3 4 weeks of NTZ or placebo, followed by 48 weeks of triple therapy (NTZ + SOC or placebo)	HCV genotype 1, treatment-naive	44% (NTZ + SOC) 32% (SOC + placebo)	

Sources:
Antaki N, Craxi A, Kamal S, et al. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. *Liver Int.* 2010 Mar;30(3):342-55.

Bacon BR, Shiffman ML, Lim JK, et al. Phase 2 randomized, double-blind, placebo-controlled study of nitazoxanide plus peginterferon and ribavirin in naive patients with chronic hepatitis C genotype 1 infection: final report [abstract 711b]. Digestive Disease Week. New Orleans, Louisiana. 1-5 May 2010.

Rossignol JF, Elfert A, El-Gohary Y, Keeffe EB. Improved virologic response in chronic hepatitis C genotype 4 treated with nitazoxanide, peginterferon, and ribavirin. *Gastroenterology.* 2009;136(3):856–62.

Shiffman ML, Ahmed A, Jacobson IM, Pruitt RE, Keeffe EB. Phase 2 randomized, double-blind, placebo-controlled study of nitazoxanide with peginterferon alfa-2a and ribavirin in nonresponders (NR) with chronic hepatitis C genotype 1: final report [abstract 296 LB]. 45th Annual Meeting of the European Association for the Study of the Liver. Vienna, Austria. 14–18 April 2010.

Boosters

Abbott is studying ABT-267, a CYP450 inhibitor, in treatment-naive people with HCV genotype 1. It is currently in phase I; in the future, this drug may be used to boost levels of other HCV—and HIV—drugs.

Immunomodulators

Monoclonal Antibodies

Monoclonal antibodies are designed to bind to a specific target, such as cell receptors or cancer cells. They attach themselves to cells that are infected, abnormal, or dying, triggering an immune response; these marked cells are then attacked. Monoclonal antibodies are also used to diagnose many conditions, deliver drugs and treat different types of cancer and autoimmune disorders. With hepatitis C, the idea behind monoclonal antibodies is to target infected cells for destruction by the immune system.

Table 22. Monoclonal Antibodies

AGENT/SPONSOR	STATUS	COMMENTS
Bavituximab Peregrine Pharmaceuticals	Phase I/II; HCV genotype 1, treatment-naive	Being studied in combination with ribavirin. Phase I studies in HCV monoinfected, all genotypes, treatment-naive, partial responders, relapsers, and nonresponders have been completed.
CT-011 Cure Tech	Phase I/II; HCV genotype 1, treatment-experienced	N/A
MBL-HCV1 Mass Biologics	Phase II; HCV genotype 1a, liver transplant recipients	N/A
Infliximab (approved for other uses) Centocor Ortho Biotech	Phase II; HCV genotype 1, treatment-naive	Used with SOC

Novel Interferon Formulations

The future role of peginterferon in HCV treatment is uncertain; nonetheless, several companies are developing novel interferons. These may be more convenient—as dosing is less frequent—or even less toxic. Researchers are also investigating devices to deliver interferon, such as an external drug pump or an implantable device for continuous infusion.

Table 23. Novel Interferon Formulations

AGENT/SPONSOR	STATUS	COMMENTS
Hanferon HanAll BioPharma	Phase I/II (slated to open in 2011); HCV genotype 1, treatment-naive	N/A
Interferon-a-2b XL Flamel Technologies	Phase II; HCV genotype 1, treatment-naive or nonresponders	Controlled-release technology; injected once weekly
Interferon 5 Digna Biotech	Phase I/II; HCV genotype 1, relapsers	Injected three times a week with or without interferon alfa-2b
Interferon lozenges Amarillo Biosciences/CytoPharm	Phase II; studied to prevent relapse in people who achieved SVR	Once daily or TID for 24 weeks

Locteron interferon Biolex Therapeutics	Phase IIb; HCV genotype 1, treatment-naive	Dosed every 2 weeks; may have more favorable side effect profile than peginterferon
PEG-IFN lambda (PEG-rIL-29) Bristol-Myers Squibb/ZymoGenet- ics	Phase II; HCV genotypes 1, 2, 3, and 4, treatment-naive (exception: 2 weeks or less of DAA monotherapy)	So far, no serious side effects or lab abnormalities reported in phase I, possibly since PEG-IFN lambda binds to a unique receptor that has less distribution throughout the body than the receptor for interferon alfa.

Therapeutic Vaccines

Some people can clear HCV without treatment (referred to as spontaneous viral clearance), through an immune response that involves HCV-specific CD4 T-cells (Lechner 2000; Thimme 2001). These same immune responses may augment HCV treatment. Researchers have developed vaccines that attempt to elicit the same immune response involved in spontaneous viral clearance of HCV, although each candidate uses a different approach.

Table 24. Therapeutic Vaccines for HCV

AGENT/SPONSOR	STATUS	COMMENTS
AdCh3NSmut and Ad6NSmut Okairos	Phase Ib; HCV genotype 1, treatment-naive	Used with SOC; prime-boost Designed to elicit cellular (CD4/ CD8) immune response
ChronVac-C Inovio/Tripep	Phase I/II; HCV genotype 1, treatment-naive, viral load of <800,000 IU/mL	Administered with a brief electri- cal pulse (called electroporation) that creates temporary pores in cell membranes, allowing the vaccine to enter cells
GI-5005 Globeimmune	Phase IIb; HCV genotype 1, treatment-naive or treatment- experienced; 40 treatment-naive people with TT genotype are being added	Used with SOC; elicits cellular responses to target and kill HCV- infected cells
IC 41 Intercell AG	Phase II; HCV genotype 1, treatment-naive (has been studied in treatment-experienced people as well)	Used alone and with SOC; given as 8 injections (just under the skin) every two weeks; stimulates T-cell responses against HCV
TG4040 Transgene	Phase I; HCV genotype 1, treatment- experienced and relapsers Phase II; HCV genotype 1, treatment- naive	6 to 13 injections with SOC; designed to elicit immune responses against hepatitis C viral proteins (NS3, NS4, and NS5B)

Immune-Based Therapies

Since the immune system is involved in spontaneous viral clearance and response to HCV treatment, researchers are pursuing numerous approaches to stimulate general, nonspecific, and HCV-specific immune responses.

Table 25. Immunomodulatory Therapies

AGENT/SPONSOR	STATUS	COMMENTS
ANA-773 (TLR-7 agonist) Anadys	Phase I	Oral; stimulating toll-like receptor 7 (TLR-7) activates nonspecific immune responses
CYT 107 (interleukin-7) Cytheris	Phase I/II; HCV genotypes 1 and 4, nonresponders	Injectable; given once weekly; IL-7 is a cytokine (a chemical messenger) involved with the development of T-cells; it helps to stimulate immune responses.
GS 9620 (TLR-7 agonist) Gilead Sciences	Phase I	N/A
IMO 2125 (TLR-9 agonist) Idera Pharmaceuticals	Phase I; HCV genotype 1, non- and null responders and treatment-naive, in combination with ribavirin	Injectable; toll-like receptor 9 (TLR-9) activates specific immune responses; twice-weekly dosing
NOV-205 Novelos	Phase II; HCV genotype 1, treatment-experienced	Injectable; given daily; unspecified immunomodulatory activity

Looking to the Future: RNA Interference

RNA interference silences genes via cellular machinery. MicroRNA (miRNA) regulates cellular genes; small interfering RNA (siRNA) specifically targets viral genes. Researchers have already identified host genes and cellular proteins that interact with HCV, making this a promising approach against hepatitis C virus.

Table 26. RNA Interference

AGENT/SPONSOR	STATUS	COMMENTS
Miravirsen Santaris Pharmaceuticals	Phase IIa; HCV genotype 1, treatment-naive	N/A
TT-33 Pfizer/Tacere	Phase I studies planned for early 2011	N/A

The Disease, Not the Virus

The focus of HCV drug development remains on curing the virus, not on preventing, delaying, or reversing liver damage from the virus. Sometimes the condition of the liver improves after SVR, but it can also remain stable or worsen. This is most apparent in people who have cirrhosis; although they have been cured, they remain at risk for hepatocellular carcinoma, and should be screened regularly.

Antifibrotic drugs will remain important, even in the DAA era. But studying these drugs is challenging, because HCV progresses slowly, and enrollment in clinical trials may be difficult, and limited to people who have not been cured (particularly those with established liver disease). Farglitazar, an initially promising antifibrotic drug, was not effective in people with HCV (McHutchison 2010b). Nonetheless, Pfizer is studying an oral anti-inflammatory drug, PF-04136309, a CCR2 antagonist which has also been studied in osteoarthritis, and other drugs of the same type are in development.

Bringing It Together: New HCV Drugs and Clinical Care

Improvements in HCV treatment are on the horizon. But stakeholders—including activists, people with HCV, and health care providers—must push to see that these drugs are studied in real-life populations, that the capacity to provide high-quality care and treatment increases, and that HCV treatment is available to all who require it.

In the United States, HCV treatment is delivered through a fragmented health care system. Undergoing treatment for hepatitis C is challenging, particularly for people with common comorbid conditions such as mental illness, substance-use disorders, and HIV. Clinicians must prepare to deliver HCV care and treatment to these patients, since they are likely to gain access to medical care with the implementation of health care reform.

Higher cure rates and shorter duration of treatment will increase HCV treatment uptake, but drug and patient-specific treatment algorithms are becoming more complex.

Although efficacy and safety are primary concerns, treatment simplicity should also be foremost. Response-guided therapy needs to be integrated into medical practice to prevent unnecessary exposure to ineffective or poorly tolerated drugs, as well as development of drug resistance. Patients must have access to information about the risks and benefits of HCV treatment, prognostic factors, side effects and strategies for their management, as well as the importance of adherence.

Thus, work must be done to prepare the health care system to deliver high-quality HCV care and treatment, and work must be done so that patients are prepared to enter the health care system to treat—and cure—their HCV.

What Treatment Action Group Does

Treatment Action Group (TAG) seeks to accelerate high-quality basic, clinical, and operational research to prevent and combat HCV. We work domestically and globally, with our activist partners, researchers, regulators, clinicians, and the pharmaceutical industry, to advance clinically relevant and ethical HCV drug development, and to secure access to HCV care and treatment for all who need it.

TAG collaborates with members of the hepatitis C community, other nonprofit organizations, researchers, service providers, clinicians, and policy makers to identify optimal models for delivery of HCV care and treatment, and to advocate for allocation of adequate resources for people living with, and at risk for, HCV.

TAG's HCV Research Recommendations

Study drugs, prior to approval, in clinically relevant populations such as African Americans, Latinos/as, people with cirrhosis, current and former drug users, people with a history of psychiatric disorders, and HIV/HCV-coinfected persons. Often, response rates from HCV clinical trials do not apply to real-life populations. HCV treatment safety, efficacy, and tolerability must be characterized in high-prevalence populations, particularly those less responsive to SOC; those at risk for rapid progression of liver disease; and those usually excluded from clinical trials. So far, enrollment of African Americans and Latinos/as in HCV treatment trials has been disappointing, hovering at approximately 10–14% (Kwo 2010; McHutchison 2009a).

TAG continues to track and document enrollment of African Americans and Latino/as in clinical trials, and pushes for sufficient enrollment of African Americans and Latino/as in HCV clinical trials. For more information, see TAG's presentation: "Do The Right Thing: Addressing Racial Disparities in Viral Hepatitis Drug Development," available at: http://www.treatmentactiongroup.org/base.aspx?id=3494 (accessed on 1 February 2011).

Numerous studies have reported that current and drug users can be safely and effectively treated with SOC, especially when they are maintained on opiate substitution treatment such as methadone and buprenorphine (Bruggmann 2008; Dore 2010; Grebely 2010; Harris 2010; Hellard 2009; Sylvestre 2007). The same is true for people with psychiatric disorders: several studies have reported that people with psychiatric disorders can be safely treated once they are offered access to ongoing mental health care (including medication, if indicated) (Martin-Santos 2008; Schaefer 2003). Since depression, mood swings, hypomania, and mania are known side effects of interferon, it is wise for clinical trials to offer a baseline psychiatric assessment, regular screening for neuropsychiatric side effects, and mental health care during clinical trials to avert treatment discontinuation.

TAG works with other activists, harm-reduction and drug-user organizations, regulatory authorities, researchers, the pharmaceutical industry, and clinicians to advocate for trials to enroll representative populations.

Hepatitis C–associated end-stage liver disease has become a leading cause of death among HIV-positive people in the United States and Western Europe, where HIV treatment is widely available (Weber 2006). HIV accelerates HCV progression, and SOC is less effective for coinfected people than for those with HCV monoinfection (see Figure 1. HCV Treatment Outcomes, page 12). Coinfected people need less toxic and more effective HCV treatments. Drug-drug interactions between DAAs and HIV drugs may limit the use of specific drugs in coinfected people; these must be fully characterized early in development to facilitate HCV treatment trials—and, ultimately, safe and effective use of DAAs in coinfected people.

TAG has co-organized multi-stakeholder meetings on HCV drug development in HIV/HCV-coinfected people with the European AIDS Community Advisory Board (ECAB). As a result of these meetings, as well as collective pressure from activists, researchers, clinicians and regulators, HCV treatment trials in HIV/HCV-coinfected people are now being launched in parallel with phase III, rather than being delayed until after approval. Trials of boceprevir and telaprevir in HIV/HCV-coinfected people are underway. Meeting reports available at: http://www.eatg.org/eatg/Scientific-Research/Conferences/Brussels-I-Sitges-III-Nov-20-2010-Brussels *(accessed 1 February 2011).*

Develop mechanisms to provide early access to DAA combination therapy for people who are ineligible for clinical trials and cannot wait for FDA approval. It is unacceptable that people with the most urgent need lack access to potentially life-saving therapies. Although preapproval access to single or multiple DAAs poses medical, administrative, and regulatory challenges, it has been done with HIV and is certainly feasible for HCV. Regulators, industry, physicians, and community members need to address and surmount barriers to early access.

In Spring 2010, TAG testified at an FDA hearing on early access to HCV treatment. TAG asked regulators to create a framework allowing access to potentially life-saving drugs for high-risk populations without endangering the development of promising drugs. We support early access to direct-acting antivirals, and will continue to work with all stakeholders on this important issue.

Study drugs in liver transplant candidates and recipients as soon as it is safe to do so. Hepatitis C is the leading indication for liver transplantation, accounting for more than 35% of all liver transplants in the United States (Thuluvath 2010). Survival after transplantation is significantly worsened by recurrent HCV, which is difficult to treat; SOC is often ineffective in, or intolerable for, transplant candidates and recipients (see Figure 8. HCV Treatment Outcomes, page 20). Liver related mortality from recurrent HCV is significantly lower among transplant recipients who have achieved SVR than among those who were untreated or unsuccessfully treated (Rendina 2010).

Transplant candidates and recipients are in desperate need of better HCV treatment; however, clinical trials of new HCV drugs in this population are generally last on the list, lagging until drugs have already been approved.

Clear regulatory guidance is needed to prod sponsors into launching studies in transplant candidates and recipients, as well as in other high-risk populations. At a 2006 FDA meeting on development of novel agents for HCV treatment, panelists recommended that "approval of an effective agent in compensated subjects should not be adversely affected by poor outcomes observed in separate studies of decompensated liver disease" (Sherman 2007).

TAG will keep pushing for the launch of HCV clinical trials in transplant candidates and recipients prior to approval, and continue to advocate for the use of more than one experimental agent in these trials, an approach that has been successful in HIV treatment.

Prioritize access to single- or multiple DAAs for trial participants in the control arms of clinical trials, and for those who did not achieve SVR. Cross-over or roll-over study designs provide access to the experimental drug for people in the control arm. This approach should be broadened to include study participants unsuccessfully treated with single- or multiple DAAs, providing that virtual monotherapy (a multidrug regimen containing only one active agent, causing rapid development of drug resistance) can be avoided. A cross-company registry of treatment-experienced trial participants should be established, and these participants should be prioritized for enrollment into trials of DAAs from novel classes.

TAG pushes for clinical trials that are designed to identify—or optimize—treatment strategies, while posing the least possible risk to study participants.

Continue to characterize resistance to all classes of DAAs. Further characterization of resistance mutations is needed to optimize HCV treatment with DAAs, although the clinical utility of resistance testing is not clear at present. Further assessment of clinical implications of HCV drug resistance is needed. One way to assess the impact of drug resistance would be to re-treat people who acquired drug resistance in monotherapy trials with the same drug, plus SOC.

TAG advocates for comprehensive study of HCV drug resistance, and works to educate people with HCV, their service providers, and the medical community about the risk of HCV drug resistance, and strategies to avert it.

TAG's HCV priorities also include:

Optimizing HCV care and treatment by giving nonspecialist providers the tools they need to successfully treat patients with HCV. TAG is working with policy partners to advocate for a standing, multidisciplinary expert panel to develop and update HCV treatment guidelines, convened by the Department of Health and Human Services, in anticipation of rapid changes in the standard of care.

Development of second- and third-line drugs effective against HCV with commonly occurring resistance mutations. Adding a single DAA increases the likelihood of SVR for treatment-experienced people, but is not 100% effective. In fact, approximately 60% of prior nonresponders did not achieve SVR after re-treatment with telaprevir plus SOC in Vertex's PROVE-3 trial (McHutchison 2010a). Thus, an increasing population of people resistant to at least one drug, or class of drugs, is likely. Cross-resistance to HCV protease inhibitors has already been reported. Sponsors should prioritize drugs with a unique resistance profile and a high genetic barrier over "me too" drugs.

Development of drugs with activity against all HCV genotypes. There are at least six HCV genotypes. Most new HCV drugs were designed to be effective against HCV genotype 1, because it is difficult to cure with peginterferon and ribavirin, and it is predominant in the United States, Western Europe, and Japan (major pharmaceutical markets). As more people with genotype 1 are cured, and immigration patterns shift, the global distribution of HCV genotypes will change. It will not be possible to eradicate HCV without safe and effective drugs for all genotypes.

Full characterization of predictors and indicators of response and nonresponse to HCV treatment across populations. Stopping rules may change as HCV treatment evolves. Reliable predictors of response will motivate people to continue HCV treatment, and facilitate reimbursement for response-guided therapy. In turn, accurate indicators of nonresponse will lower the risk of resistance, spare people from unnecessary treatment and its side effects, and save money.

Establishment of an HCV research network. It is time to scale up HCV research capacity. The opportunity to address key clinical questions in the next five to seven years must not be squandered while sponsors prioritize getting drugs to market in the current highly competitive arena.

HCV treatment is complex, and a dedicated research network could advance crucial areas, such as exploration of multi-experimental agent trials, population-specific questions, studies of best-in-class drug combinations, and development and optimization of HCV treatment strategies, particularly for hard-to-treat populations. These are likely to languish without a public/private research network. This has been a fruitful approach in HIV disease, where policy makers have allocated funds, and sponsors

have contributed drugs and diagnostics. In the meantime, regulators, researchers, sponsors, and community members need to continue the dialogue on launching cross-company collaborations.

Investigation of DAAs for HCV Prophylaxis. There is no postexposure prophylactic strategy for hepatitis C, regardless of exposure type. HCV transmission from occupational exposures ranges from 0.2% to 10% (Corey 2009). Clearly, research is warranted on the efficacy of oral antiviral agents for postexposure prophylaxis for occupational and nonoccupational exposures, and for persons about to undergo liver transplantation.

Access to Treatment
TAG works domestically and internationally, in partnership with other activists, to push for access to HCV care and treatment for all who need it.

Quality of Treatment
TAG continues to highlight and promote the work of pioneering clinicians and researchers.

Resources

ClinicalTrials.gov (www.clinicaltrials.gov) (accessed on 1 February 2011) provides information on HCV drug development and research.

HCV Advocate (www.hcvadvocate.org) (accessed on 1 February 2011) offers conference reporting, and an up-to-date HCV pipeline chart, available on line at:
http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs.html.

HIV and Hepatitis.com (www.hivandhepatitis.com) (accessed on 1 February 2011) offers news and conference reports.

NATAP (National AIDS Treatment Advocacy Project) (www.natap.org) (accessed on 1 February 2011) offers comprehensive HCV coverage.

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