# THE HEPATITIS C TREATMENT PIPELINE REPORT

PROTEASE INHIBITORS • ABT-450 • ACH-0141625 • BI 201355
BMS-650032 • BOCEPREVIR • CTS-1027 • DANOPREVIR • GS 9256
GS 9451 • IDX 320 • MK-5172 • TELAPREVIR • TMC435350 • VANIPREVIR
VX-985 • NS5A INHIBITORS • AZD7295 • BMS-790052 • BMS-824393 • CF102
GS 5885 • PPI-461 • POLYMERASE INHIBITORS • ABT-333 • ABT-072 • ANA598
BI 207127 • BMS-791325 • FILIBUVIR • IDX184 • IDX375 • INX-189 • PSI-7977
PSI-352938 • RG7128 • RG7348 • TEGOBUVIR • VX-222 • VX-759
CYCLOPHILIN INHIBITORS • DEBIO 025 • SCY-635 • SILIBININ • LEGALON
SILYMARIN • CLEMIZOLE • ITX 5061 • SERINE C-PALMITOYLTRANSFERASE
INHIBITOR • SPC3649 • NITAZOXANIDE • MONOCLONAL ANTIBODIES
BAVITUXIMAB • CT-011 • MBL-HCV1 • INFLIXIMAB • NOVEL INTERFERONS
JOULFERON/ZALBIN • HANFERON • INTERFERON-A-2B XL • INTERFERON 5
INTERFERON LOZENGES • LOCTERON INTERFERON • PEG-IFN LAMBDA
THERAPEUTIC VACCINES • ADCH3NSMUT • AD6NSMUT • CHRONVAC-C
GI-5005 • IC 41 • TG4040 • IMMUNOMODULATORS • ANA-773 • CYT 107
GS 9620 • IMO 2125 • NOV-205 • RNA INTERFERENCE • MIRAVIRSEN • TT-33

BY TRACY SWAN

TREATMENT ACTION GROUP
MARCH 2011

## ABOUT TAG

TAG's Hepatitis/HIV Project draws from the core values and history of HIV activism, while incorporating hepatitis C-specific information into strategies targeting different constituencies, regions, and countries. In 2011, the Hepatitis/HIV Project will focus on optimizing quality of, and broadening access to HCV care and treatment for communities and individuals by continuing its domestic and international work with other activists, regulatory agencies, pharmaceutical companies, clinicians and the patient community.


ACKNOWLEDGMENTS

Thanks to:

Andrea Benzacar, Editor
Mark Harrington and Scott Morgan, Assistant Editors
Lei Chou, Graphic Design and Layout
Joseph Mc Connell, Administrative Support

Treatment Action Group's Board and generous donors:
without you, this work would not have been possible.


**Hepatitis C Treatment Pipeline Report**




ISBN 978-0-9819863-7-1
permission to use w/o copyright



Treatment Action Group
611 Broadway Suite 308
New York, NY 10012
www.treatmentactiongroup.org

Tel:1-212-253-7922
Fax:1-212-253-7923

# THE HEPATITIS C TREATMENT PIPELINE REPORT

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**
New York, New York

March 2011

# TABLE OF CONTENTS

[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).

## TERMS FOR HCV MILESTONES AND POPULATIONS

### **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).

## TERMS FOR HCV MILESTONES AND POPULATIONS (CONT.)

### 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)*<br>Race/ethnicity (Asian >Caucasian >Latino/a >African American)<br>(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<br>(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<br>(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<br>27% Faculty practice<br>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:<br>28.9% Overall<br>10.1% African American<br>Weight-based RBV:<br>34% Overall<br>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<br>41% Non-cirrhotic |

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

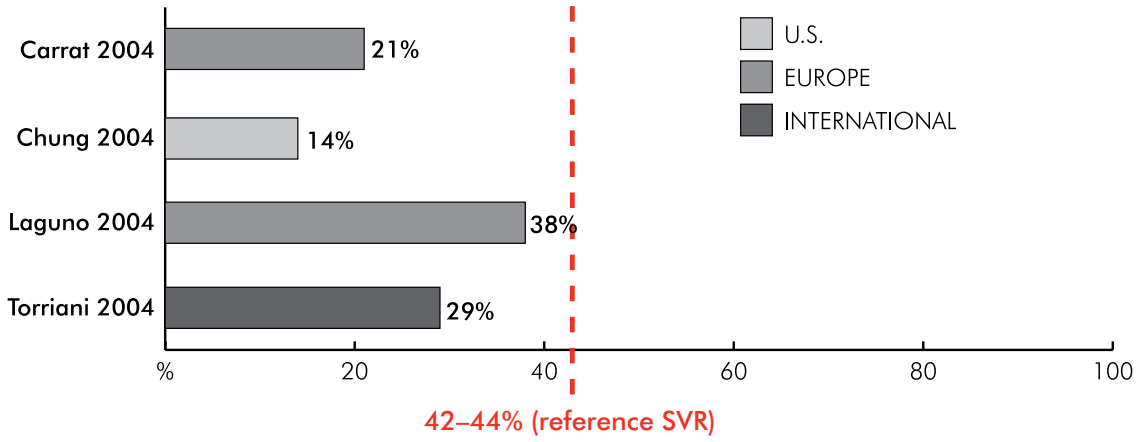
## HIV/HCV Coinfection

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)**



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.

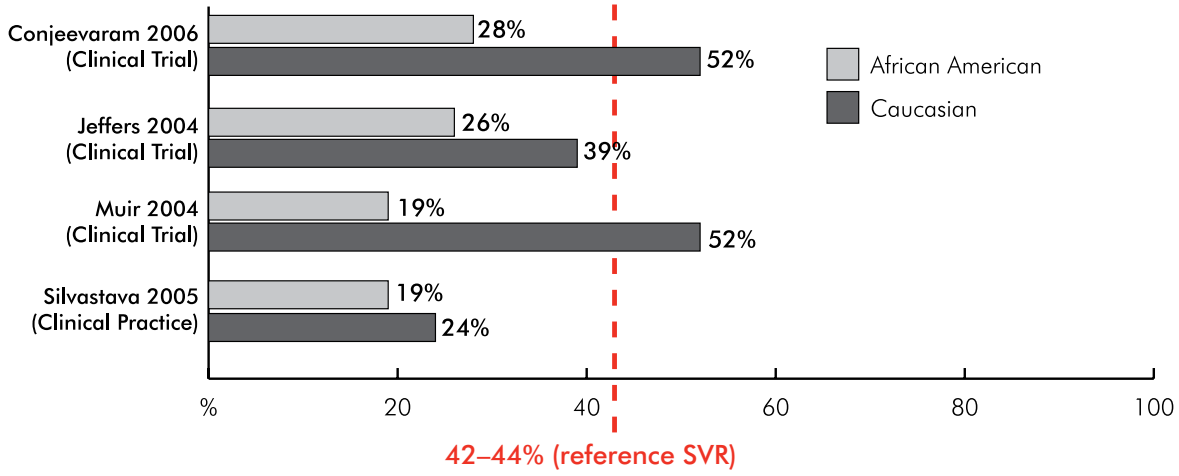
a: hyperbilirubinemia
b: CYP3A4-mediated
c: guanosine analogue competition
d: mitochondrial toxicity
e: phosphorylation inhibition
f: hematological toxicity, anemia
g: overlapping toxicity, anemia
h: CYP3A4 competition

## 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

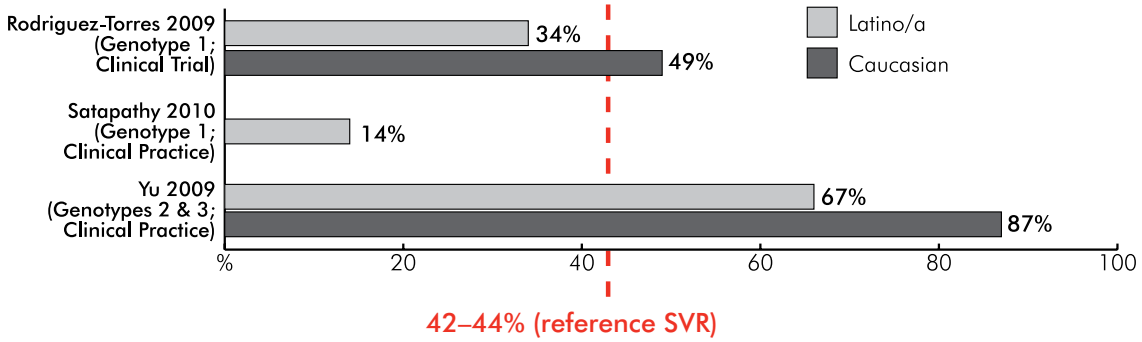
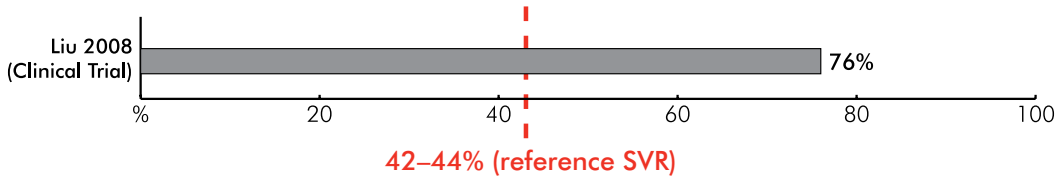


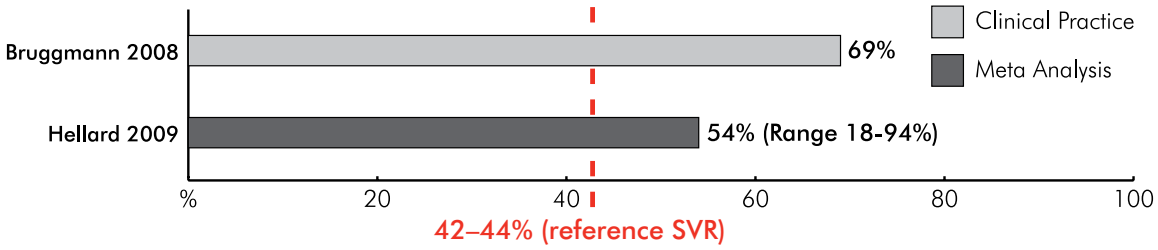

Figure 4. HCV Treatment Outcomes, Asian (Genotype 1)




## 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.

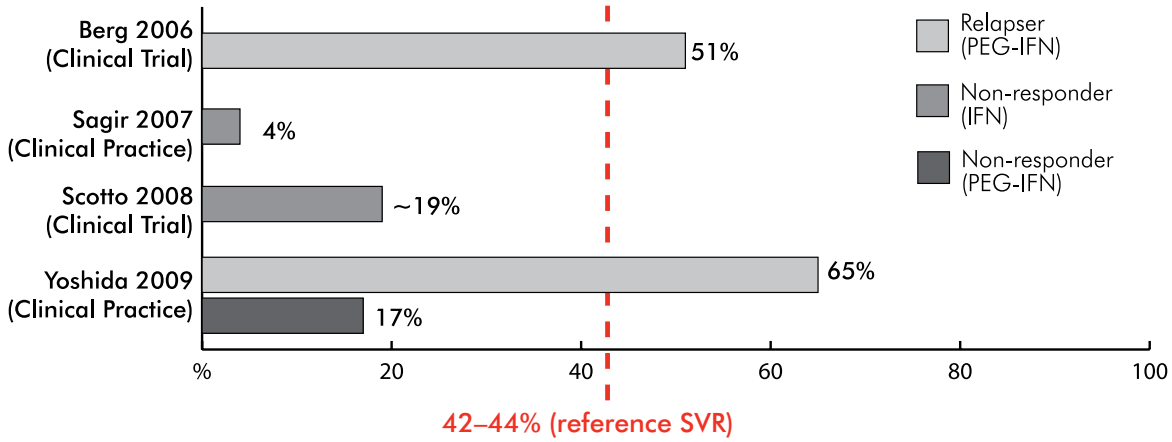
Figure 5. HCV Treatment Outcomes, Injection Drug Users



## 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.

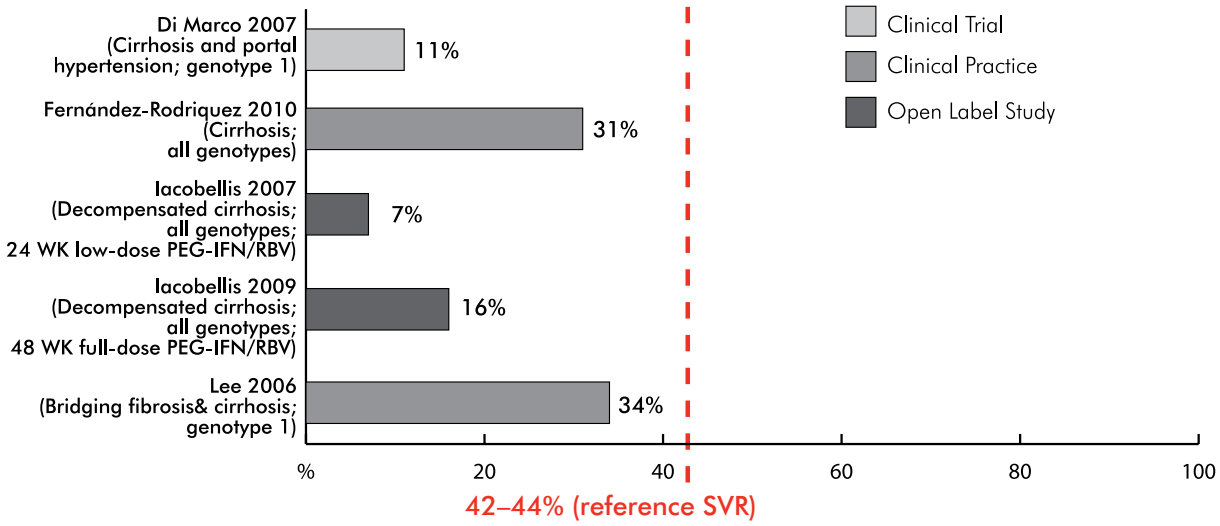
**Figure 6. HCV Treatment Outcomes by Prior Treatment Response**




## 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.

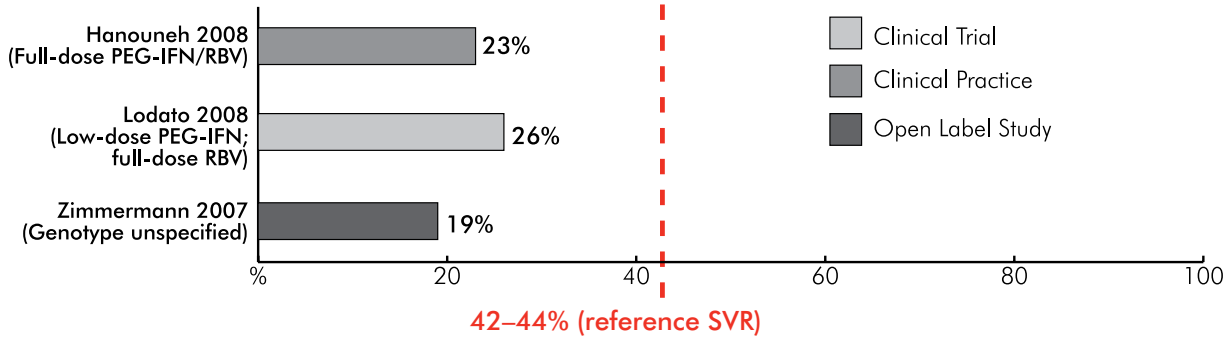
## Transplant Candidates and Recipients

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)




## 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 $\geq$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<br>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<br>Achillion | Phase II; genotype 1, treatment-naive | Once-daily dosing |
| BI 201355<br>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<br>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<br>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<br>Conatus | Phase II; genotype 1, null responders | 24-week study with SOC |
| Danoprevir (formerly ITMN-191 and RG7227)<br>Genentech/Roche | Phase I; genotype 1, treatment-naive<br>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<br>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<br>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<br>Merck | Phase I; genotypes 1 & 3 (males only) | Demonstrated activity against resistant virus in lab studies and chimps |
| Vaniprevir (MK-7009)<br>Merck | Phase II; genotype 1, treatment-experienced | A phase II trial in treatment-naive people with HCV genotype 1 was withdrawn |
| Telaprevir<br>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<br>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<br>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<br>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<br><br>Dysgeusia (bad or metallic taste in the mouth) |
| | | **48 weeks** of triple therapy vs. 4-week lead-in with PEG-IFN/RBV, respectively | 67–75% | |
| Boceprevir **SPRINT-2** | TID<br>12 pills/day | **28–48 weeks RGT**: 4-week lead-in with PEG-IFN/RBV; add BOC.<br><br>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.<br><br>Duration of treatment varies according to response at weeks 8 and 24.<br><br>Treatment paradigm is designed to optimize SVR in an easy-to-treat population. |
| Telaprevir **PROVE 1** | Q8 hrs*<br>6 pills/day | **24 weeks**:<br>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;<br><br>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;<br><br>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.<br><br>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.<br><br>If HCV RNA is undetectable at weeks 8 and 24, stop treatment at week 28;<br><br>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<br>74% for 48 weeks |
| Week 12 | Treat for 48 or 72 weeks | 49% for 48 weeks<br>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<br>**RESPOND-2**<br><br>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%<br>Relapse: 68.6%<br>Nonresponse: 40.4% | Serious adverse events more common in BOC arms (10–14% vs. 5% for SOC)<br><br>Epoetin alfa was used by 41–46% of those in the BOC arms<br><br>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%<br>Relapse: 74.8%<br>Nonresponse: 51.7% | |
| | 4-week PEG-IFN/RBV lead-in, then PEG-IFN/RBV+placebo for 44 weeks | Overall: 21%<br>Relapse: 29.4%<br>Nonresponse: 6.9% | |
| Telaprevir Phase II<br>**PROVE 3**<br><br>Prior relapse, breakthrough, and nonresponse | TP+PEG-IFN/RBV for 12 weeks, then PEG-IFN/RBV for 12 weeks | Overall: 51%<br>Relapse: 69%<br>Prior breakthrough: 57%<br>Nonresponse: 39% | Treatment-experienced patients need 48 weeks of treatment.<br><br>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%<br>Relapse: 76%<br>Breakthrough: 62%<br>Nonresponse: 38% | |
| | TP+PEG-IFN/RBV for 24 weeks | Overall: 24%<br>Relapse: 42%<br>Breakthrough: 36%<br>Nonresponse: 11% | |
| | PEG-IFN/RBV+placebo for 48 weeks | Overall: 14%<br>Relapse: 20%<br>Breakthrough: 40%<br>Nonresponse: 9% | |
| Telaprevir Phase III<br>**REALIZE**<br><br>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%<br>Relapse: 88%<br>Partial response: 54%<br>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%<br>Relapse: 83%<br>Partial response: 59%<br>Null response: 29% | |
| | PEG-IFN/RBV+placebo for 48 weeks | Overall 17%<br>Relapse: 24%<br>Partial response: 15%<br>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.

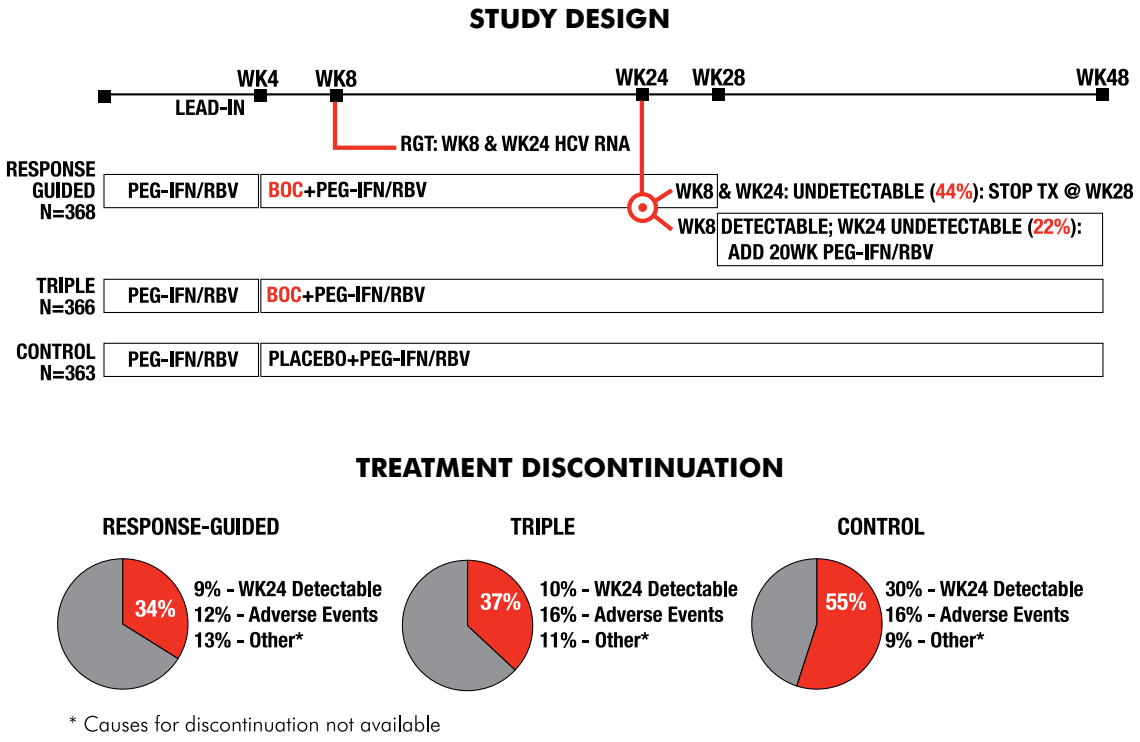
The most problematic boceprevir side effect is anemia (defined as hemoglobin [HgB] <10 grams per deciliter [g/dL]). In HCV SPRINT-1, a phase II trial in treatment-naive people with HCV genotype 1, more than half of the participants treated with boceprevir developed anemia (vs. 34% of the control arm). 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).

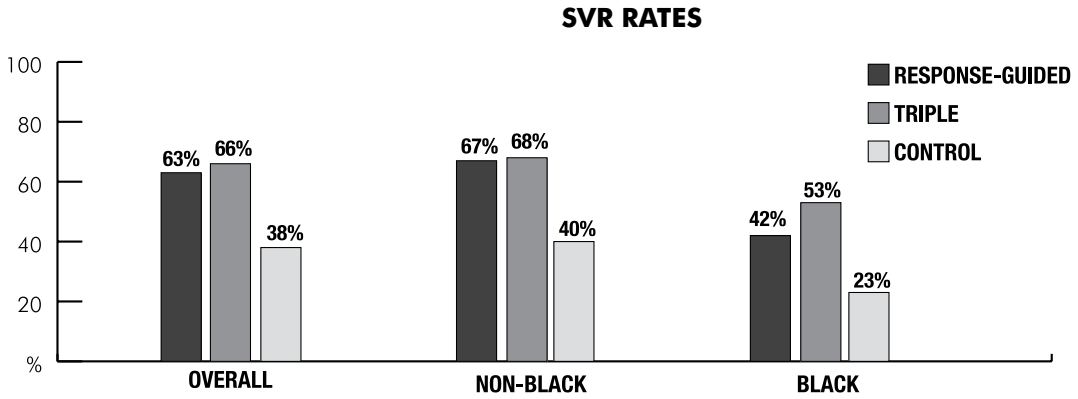
### EPOETIN ALFA

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)




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-development/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

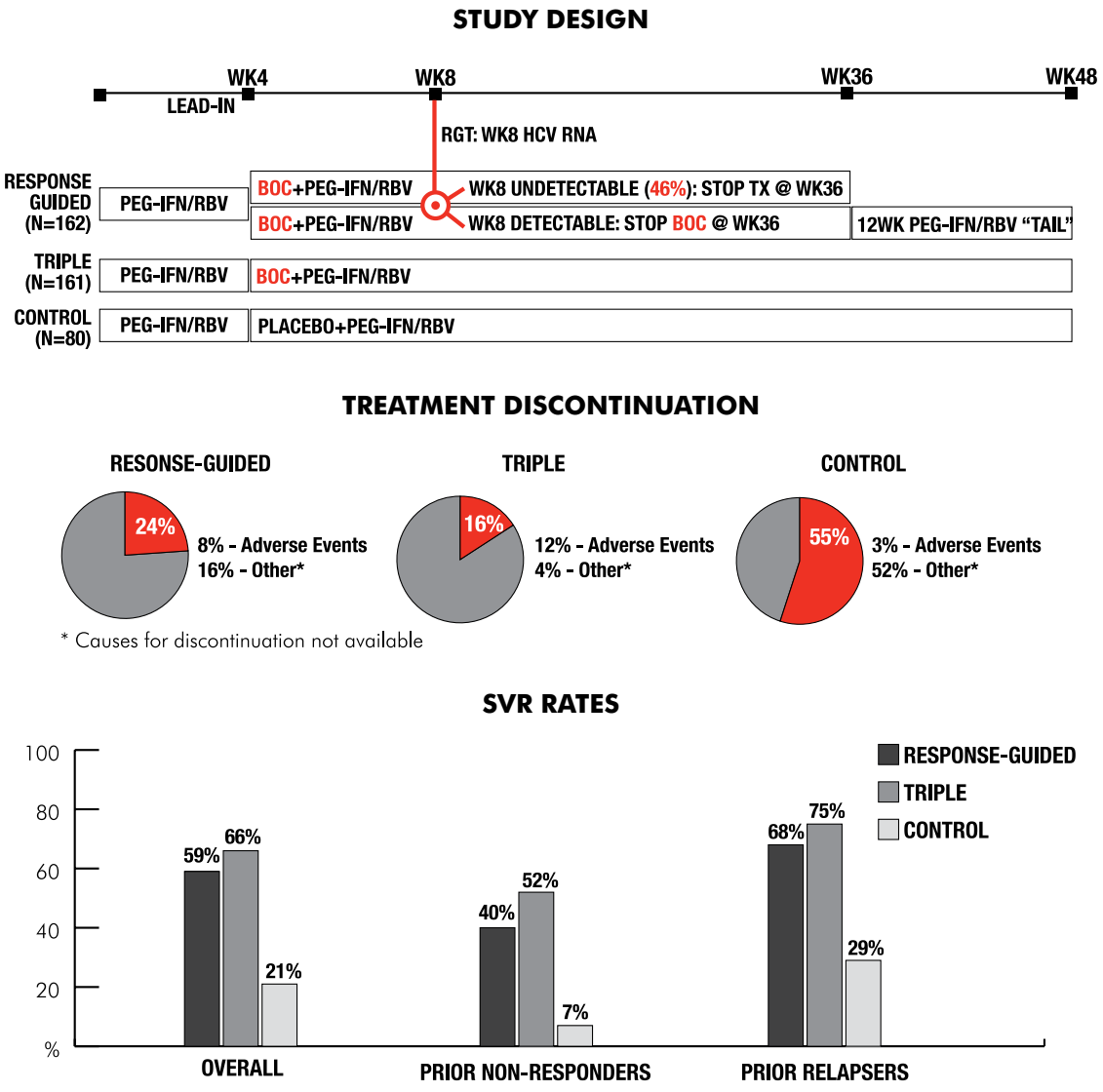
Results of RESPOND-1, the boceprevir phase II trial in non- and null responders, are very difficult to interpret due to significant changes in the protocol during the trial (adding ribavirin to all study arms and increasing boceprevir dose); the highest SVR rate was only 14% (Schiff 2008).

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)




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).

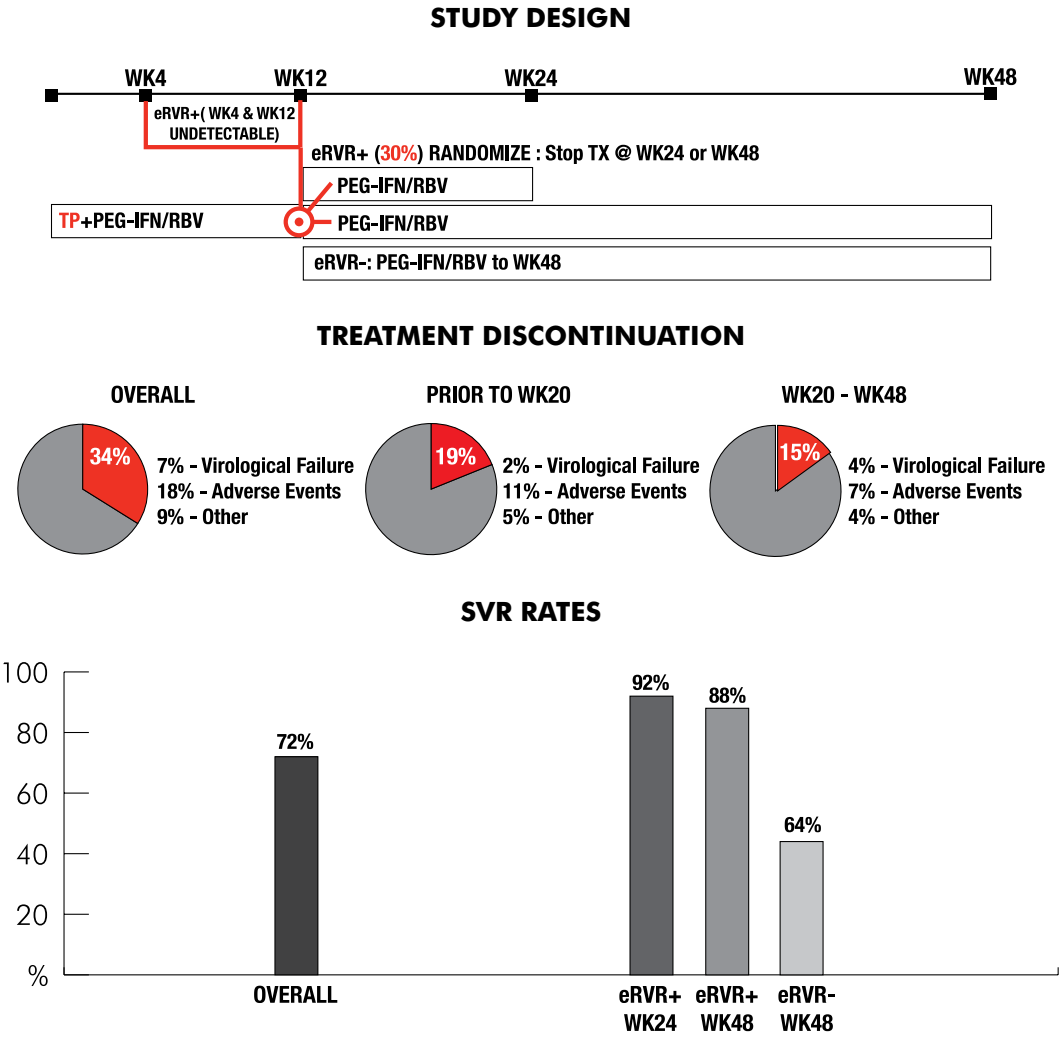
## Telaprevir in Treatment-Naive People

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.

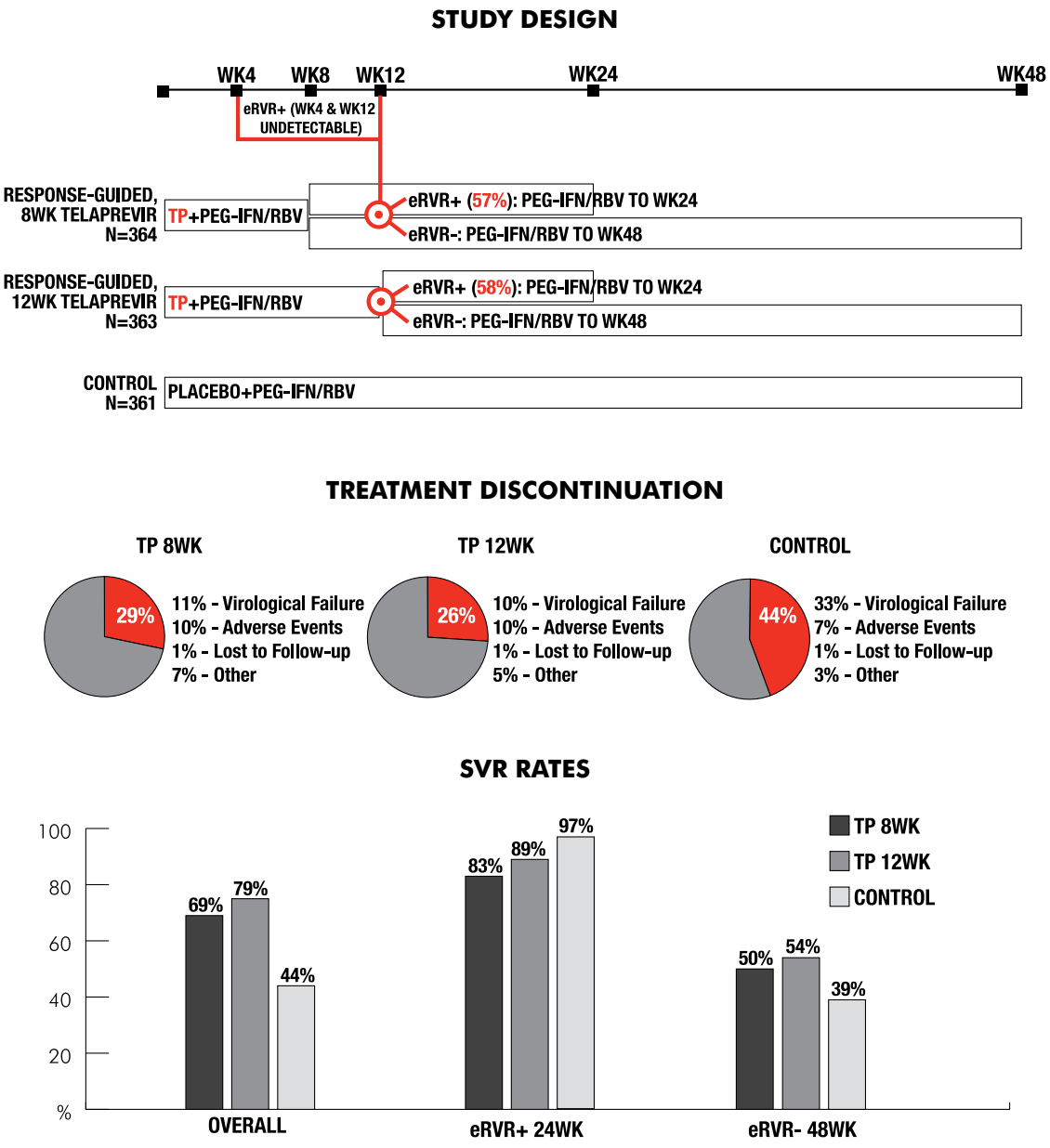
Figure 11. ILLUMINATE: Telaprevir Phase III (Treatment-Naive; N=540)



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)



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/releasedetail.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**<br>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:**<br>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 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.

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**<br>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)<br>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**<br>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)<br>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**<br>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)<br>F3 and F4 combined | SVR not reported by liver histology |
| **SPRINT-2**<br>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)<br>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<br>Arrow Therapeutics/<br>AstraZeneca | Phase II | Future of this compound is uncertain, as sponsor is ceasing HCV drug development |
| BMS-790052<br>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<br><br>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<br><br>Study in HCV genotypes 1 and 4, treatment-naive, and nonresponders with HCV genotype 1 |
| BMS-824393<br>Bristol-Myers Squibb | Phase II; HCV genotype 1, treatment-naive | N/A |
| CF102<br>Can-Fite | Phase I/II; HCV genotype 1 | Also being studied as a treatment for liver cancer |
| GS 5885<br>Gilead Sciences | Phase I; HCV genotype 1, treatment-naive | N/A |
| PPI-461<br>Presidio | Phase Ib; HCV genotype 1, treatment-naive | Has pan-genotypic activity in lab testing; may be once-daily |

## 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<br>Abbott | Phase I/II; HCV genotype 1; healthy volunteers and treatment-naive | N/A |
| ABT-072<br>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<br>Anadys | Phase II; HCV genotype 1, treatment-naive | BID |
| BI 207127<br>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<br>Bristol-Myers Squibb | Phase II; HCV genotype 1, treatment-naive | N/A |
| Tegobuvir (GS 9190)<br>Gilead Sciences | Phase II; HCV genotype 1, treatment-naive | Being studied with GS 9256, an HCV protease inhibitor and SOC<br>Also being studied in combination with GS 9451, an HCV protease inhibitor, with SOC |
| IDX375<br>Idenix | Phase I; healthy volunteers | Possibly once- or twice-daily dosing |
| Filibuvir (PF-00868554)<br>Pfizer | Phase II; HCV genotype 1, treatment-naive | N/A |
| VX-222<br>Vertex | Phase II; HCV genotype 1, treatment-naive | Also being studied in combination with telaprevir |
| VX-759<br>Vertex | Phase II; HCV genotype 1, treatment-naive | N/A |
| **NUCLEOSIDES AND NUCLEOTIDES** | | |
| IDX184 (nucleotide)<br>Idenix | Phase II; HCV genotype 1, treatment-naive | Clinical hold removed; phase II will be launched in mid-2011 |
| INX-189 (nucleotide)<br>Inhibitex | Phase I; healthy volunteers | Possibly once-daily dosing |
| PSI-7977 (nucleotide)<br>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<br>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)<br>Pharmasset | Phase I; HCV genotype 1 | N/A |

| | | |
|---|---|---|
| RG7128 (nucleoside)<br>Roche/Genentech | Phase II;<br>HCV genotypes 1 and 4, treatment-naive; also studied in nonresponders with HCV genotypes 2 and 3 | BID |
| RG7348 (nucleoside)<br>Roche/Genentech | Phase I; HCV genotype 1, treatment-naive | N/A |
| TMC 649128 (nucleoside)<br>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<br>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.<br>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<br>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)<br>Medical University of Vienna | Phase II; all genotypes, nonresponders with SOC, or prior nonresponders as monotherapy | Daily infusions for 21 days plus SOC; different infusion schedules for silibinin monotherapy |
| Legalon (capsules)<br>National Center for Complementary and Alternative Medicine (NCCAM) | Phase II; treatment-experienced | TID for 24 weeks |
| Legalon (capsules)<br>University of Maryland | Phase II/III; acute hepatitis C | TID for 4 weeks |
| Silymarin plus green tea extract (capsules)<br>University of North Carolina–Chapel Hill | Phase I/II; all HCV genotypes, treatment-naive | Single site in North Carolina |
| Silymarin<br>Buckwang Pharmaceuticals | Phase III; treatment experienced, HCV genotype not specified | Single site in Seoul, Korea |
| Silymarin (capsules)<br>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<br>Eiger BioPharmaceuticals | Phase I; HCV genotypes 1 and 2, treatment-naive | Anti-itching drug with activity against HCV |
| ITX 5061<br>iTherX | Phase I; HCV genotype 1, treatment-naive | Entry inhibitor |
| Serine C-palmitoyltransferase inhibitor (injection)<br>Chugai/Roche/Genentech | Phase I | May inhibit HCV replication by interfering with HCV NS5A and lipid cell membranes |
| SPC3649 (injection)<br>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<br>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)<br>79% (NTZ + SOC)<br>50% (SOC) | In genotype 4, SVR ranges from 43% to 70% with SOC |
| STEALTH C-2<br>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)<br>0% (SOC + placebo) | Missing data on response to prior treatment in 20% |
| STEALTH C-3<br>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)<br>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<br>Peregrine Pharmaceuticals | Phase I/II; HCV genotype 1, treatment-naive | Being studied in combination with ribavirin.<br>Phase I studies in HCV monoinfected, all genotypes, treatment-naive, partial responders, relapsers, and nonresponders have been completed. |
| CT-011<br>Cure Tech | Phase I/II; HCV genotype 1, treatment-experienced | N/A |
| MBL-HCV1<br>Mass Biologics | Phase II; HCV genotype 1a, liver transplant recipients | N/A |
| Infliximab (approved for other uses)<br>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<br>HanAll BioPharma | Phase I/II (slated to open in 2011); HCV genotype 1, treatment-naive | N/A |
| Interferon-a-2b XL<br>Flamel Technologies | Phase II; HCV genotype 1, treatment-naive or nonresponders | Controlled-release technology; injected once weekly |
| Interferon 5<br>Digna Biotech | Phase I/II; HCV genotype 1, relapsers | Injected three times a week with or without interferon alfa-2b |
| Interferon lozenges<br>Amarillo Biosciences/CytoPharm | Phase II; studied to prevent relapse in people who achieved SVR | Once daily or TID for 24 weeks |

| | | |
|---|---|---|
| Locteron interferon<br>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)<br>Bristol-Myers Squibb/ZymoGenetics | 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<br>Okairos | Phase Ib; HCV genotype 1, treatment-naive | Used with SOC; prime-boost Designed to elicit cellular (CD4/CD8) immune response |
| ChronVac-C<br>Inovio/Tripep | Phase I/II; HCV genotype 1, treatment-naive, viral load of <800,000 IU/mL | Administered with a brief electrical pulse (called electroporation) that creates temporary pores in cell membranes, allowing the vaccine to enter cells |
| GI-5005<br>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<br>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<br>Transgene | Phase I; HCV genotype 1, treatment-experienced and relapsers<br>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)<br>Anadys | Phase I | Oral; stimulating toll-like receptor 7 (TLR-7) activates nonspecific immune responses |
| CYT 107 (interleukin-7)<br>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)<br>Gilead Sciences | Phase I | N/A |
| IMO 2125 (TLR-9 agonist)<br>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<br>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<br>Santaris Pharmaceuticals | Phase IIa; HCV genotype 1, treatment-naive | N/A |
| TT-33<br>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.

# ENDNOTES


Ahmed-Belkacem A, Ahnou N, Barbotte L, et al. Silibinin and related compounds are direct inhibitors of hepatitis C virus RNA-dependent RNA polymerase. *Gastroenterology*. 2010 Mar;138(3):1112-22.

Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol. 2006;44(1 Suppl):S6-9.
Ansaldi F, Bruzzone B, Testino G, et al. Combination hepatitis C virus antigen and antibody immunoassay as a new tool for early diagnosis of infection. *J Viral Hepat*. 2006 Jan;13(1):5-10.

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.

Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006 May 16;144(10):705-14.

Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon Alfa-2a Plus Ribavirin Is More Effective Than Peginterferon Alfa-2b Plus Ribavirin for Treating Chronic Hepatitis C Virus Infection. *Gastroenterology* 2010;138:116–122.

Backus LI, Boothroyd D, Deyton LRHIV, hepatitis C and HIV/hepatitis C virus co-infection in vulnerable populations. *AIDS*. 2005 Oct;19 Suppl 3:S13-9.

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 boveprevir 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.

Bani-Sadr F, Lapidus N, Bedossa P, et al; French National Agency for Research on AIDS; Viral Hepatitis-HC02-Ribavic Study Team. Progression of fibrosis in HIV and hepatitis C virus-coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors. *Clin Infect Dis*. 2008 Mar 1;46(5):768-74.

Bell BP, Manos MM, Zaman A, et al. The epidemiology of newly diagnosed chronic liver disease in gastroenterology practices in the United States: results from population-based surveillance. *Am J Gastroenterol*. 2008 Nov;103(11):2727-36

Berg T, Mc Hutchison JG, Adda N, et al. SVR with telaprevir, peginterferon-alfa2a and ribavirin in HCV patients with well-characterized prior null response, partial response, viral breakthrough or relapse after PR: rollover study 107. [abstract 108] 45th Annual Meeting of the European Association for the Study of the Liver. Vienna, Austria. 14-18 April, 2010.

Bernier L, Willems B, Delage G, Murphy DG. Identification of numerous hepatitis C virus genotypes in Montreal, Canada. *J Clin Microbiol*. 1996 Nov;34(11):2815-8.

Biermer M, Berg T. Rapid suppression of hepatitis C viremia induced by intravenous silibinin plus ribavirin. *Gastroenterology*. 2009 Jul;137(1):390-1.

Blackard JT, Yang Y, Bordoni P, Sherman KE, Chung RT; AIDS Clinical Trials Group 383 Study Team. Hepatitis C virus (HCV) diversity in HIV-HCV-coinfected subjects initiating highly active antiretroviral therapy. *J Infect Dis*. 2004 Apr 15;189(8):1472-81.

Bonnard P, Lescure FX, Amiel C, et al. Documented rapid course of hepatic fibrosis between two biopsies in patients coinfected by HIV and HCV despite high CD4 cell count. *J Viral Hepat*. 2007 Nov;14(11):806-11.

Bräu N, Rodriguez-Torres M, Prokupek D, et al. Treatment of chronic hepatitis C in HIV/HCV-coinfection with interferon alpha-2b+ full-course vs. 16-week delayed ribavirin. *Hepatology*. 2004 Apr;39(4):989-98.

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.

Bruggmann P, Falcato L, Dober S, et al. Active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients. *J Viral Hepat*. 2008 Oct;15(10):747-52

Butt AA, Khan UA, Shaikh OS, et al. Rates of HCV treatment eligibility among HCV-monoinfected and HCV/HIV-coinfected patients in tertiary care referral centers. *HIV Clin Trials*. 2009 Jan-Feb;10(1):25-32

Butt AA, McGinnis KA, Skanderson M, Justice AC. Hepatitis C treatment completion rates in routine clinical care. *Liver Int*. 2010 Feb;30(2):240-50.

Cachafeiro SP, Lewden C, Hernando V, et al; CoRIS/CoRIS-MD All-cause Mortality in HIV-infected Patients in Spain Compared to the General Population according to HCV Status. [abstract 650] 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, California. 16-19 February, 2010.

Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol*. 2010 May;52(5):652-7.

Carrión JA, Martínez-Bauer E, Crespo G, et al. Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: A retrospective study. *J Hepatol*. 2009 Apr;50(4):719-28.

Cenci M, Massi M, Alderisio M, De Soccio G, Recchia O. Prevalence of hepatitis C virus (HCV) genotypes and increase of type 4 in central Italy: an update and report of a new method of HCV genotyping. *Anticancer Res*. 2007 Mar-Apr;27(2):1219-22.

Centers for Disease Control and Prevention (CDC). Hepatocellular carcinoma - United States, 2001-2006. *MMWR Morb Mortal Wkly Rep*. 2010 May 7;59(17):517-20.

Chen TY, Ding EL, Seage Iii GR, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clin Infect Dis*. 2009 Nov 15;49(10):1605-15.

Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Overview of patient compliance with medication dosing: a literature review. *Clin Ther*. 2001 Aug;23(8):1296-310.

Conjeevaram HS, Fried MW, Jeffers LJ, Terrault et al; Virahep-C Study Group. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology*. 2006 Aug;131(2):470-7.

Corey KE, Servoss JC, Casson DR, et al. Pilot study of postexposure prophylaxis for hepatitis C virus in healthcare workers. *Infect Control Hosp Epidemiol*. 2009 Oct;30(10):1000-5.

Cournot M, Glibert A, Castel F, et al. Management of hepatitis C in active drugs users: experience of an addiction care hepatology unit. *Gastroenterol Clin Biol*. 2004 Jun-Jul;28 (6-7 Pt 1):533-9.

Craxi A, Zuckerman E, Koutsounas S, et al.) PREDICT Study Final Results: Efficacy and Patients With Chronic Hepatitis C Virus (HCV) Genotype 1 (G1) With Low Viral Load Who Achieve Rapid Viral Response. [abstract 832] 60th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 30 October –1 November, 2009.

Crippin JS, McCashland T, Terrault N, Sheiner P, Charlton MR. A pilot study of the tolerability and efficacy of antiviral therapy in hepatitis C virus-infected patients awaiting liver transplantation. *Liver Transpl*. 2002 Apr;8(4):350-5.

Darling J, Aerssens J, Fanning G, et al. Quantitation of pre-treatment serum IP-10 improves the predictive value of an IL28B gene polymorphism for hepatitis C treatment response. [abstract 128] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October –2 November, 2010.

*Datamonitor*. Pipeline and Commercial Insight: Hepatitis C - High unmet need drives rapid innovation. Available at: http://www.datamonitor.com/store/product/hepatitis_c_market_forecast?productid=IMHC0217 2009. (Accessed on 2 February 2011).

Daruich J, Kikuchi L, Kaplan DE, et al. Increasing incidence of hepatocellular carcinoma in HIV-infected patients. A pilot study in 7 countries in north and south America and Europe. [abstract 1831] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October – 2 November, 2010.

Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology. 2004 Nov;127(5):1372-80.

Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of the Hepatitis C Virus (HCV)-Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression. *Gastroenterology* 2010 Feb;138 (2):513-21.

de Castro IF, Micheloud D, Berenguer J, et al. Hepatitis C virus infection is associated with endothelial dysfunction in HIV/hepatitis C virus coinfected patients. *AIDS*. 2010 Aug ;24(13):2059-67.

Delwaide J, Gerard C, Reenaers C, et al; Groupe Liegeois D'etudes Des Virus Hepatotropes (GLEVE). Hepatitis C virus genotype 5 in southern belgium: epidemiological characteristics and response to therapy. *Dig Dis Sci*. 2005 Dec;50(12):2348-51.

De Meyer S, Ghys A, et al. (abstract 95) Analyses of genotype 2/3 HCV variants in patients treated with telaprevir in study C209 showed that telaprevir resistance profile appears to be consistent across genotypes. *Antiviral Therapy* 2010; 15 Suppl 2:A118.

Deng LP, Gui XE, Zhang YX, Gao SC, Yang RR. Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *World J Gastroenterol*. 2009 Feb 28;15(8):996-100.

Desmond CP, Roberts SK, Dudley F, et al. Sustained virological response rates and durability of the response to interferon-based therapies in hepatitis C patients treated in the clinical setting. *J Viral Hepat*. 2006 May;13(5):311-5.

Diago M, Castellano G, García-Samaniego J, et al. Association of pretreatment serum interferon gamma inducible protein 10 levels with sustained virological response to peginterferon plus ribavirin therapy in genotype 1 infected patients with chronic hepatitis C. *Gut*. 2006 Mar;55(3):374-9.

DiBonaventura MD, Yuan Y, L'Italien G, Kim R. The impact of hepatitis C on health-related quality of life, work productivity and healthcare utilization. [abstract 1942] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October – 2 November, 2010.

Donlin MJ, Cannon NA, Aurora R, et al; Virahep-C Study Group. Contribution of genome-wide HCV genetic differences to outcome of interferon-based therapy in Caucasian American and African American patients. *PLoS One*. 2010 Feb 3;5(2):e9032

Dore GJ, Hellard M, Matthews GV, et al; Australian Trial In Acute Hepatitis C Study Group. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. *Gastroenterology*. 2010 Jan;138(1):123-35.e1-2

Dryer PD, Limketkai BN, Martin CM, et al. Screening for hepatitis C virus non-nucleotide resistance mutations in treatment-naive women. *J Antimicrob Chemother*. 2009 Nov;64(5):945-8

Dusheiko G; Caruntu FA, M Bourliere, et al. Baseline characteristics and week 4 response among chronic hepatitis C patients infected with HCV genotype 1, 2, 3, or 4: interim results of the Prophesys trial. [abstract 486] 44th Annual Meeting of the European Association for the Study of the Liver. Copenhagen, Denmark. 22-26 April, 2009.

European AIDS Clinical Society. *Clinical Management and Treatment of HIV Infected Adults in Europe*. Version 5 5http://www.europeanaidsclinicalsociety.org/guidelinespdf/1_Treatment_of_HIV_Infected_Adults.pdf (Acessed 2 February 2011).

Everson GT, Hoefs JC, Seeff LB, et al; HALT-C Trial Group. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial. *Hepatology*. 2006 Dec;44(6):1675-84.

Ferenci P, Laferl H, Scherzer TM, et al; Austrian Hepatitis Study Group. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. *Gastroenterology*. 2008 Aug;135(2):451-8(a).

Ferenci P, Scherzer TM, Kerschner H, et al. Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy. *Gastroenterology*. 2008 Nov;135(5):1561-7(b).

Fernández I, Castellano G, Domingo MJ, et al. Influence of viral genotype and level of viremia on the severity of liver injury and the response to interferon therapy in Spanish patients with chronic C infection. *Scand J Gastroenterol*. 1997 Jan;32(1):70-6.

Fernández-Rodríguez CM, Alonso S, Martinez SM, et al. Peginterferon Plus Ribavirin and Sustained Virological Response in HCV-Related Cirrhosis: Outcomes and Factors Predicting Response. *Am J Gastroenterol*. 2010 Aug 10.

Feuerstadt P, Bunim AL, Garcia H, et al. Effectiveness of hepatitis C treatment with pegylated interferon and ribavirin in urban minority patients. *Hepatology*. 2010 Apr;51(4):1137-43.

Flisiak R, Feinman SV, Jablkowski M, et al. The cyclophilin inhibitor Debio 025 combined with PEG IFNalpha2a significantly reduces viral load in treatment-naïve hepatitis C patients. *Hepatology*. 2009 May;49(5):1460-8.

Food and Drug Administration. Public Health Advisory: erythropoiesis-stimulating agents (ESAs). March 9, 2007. Available at: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm124262.htm. Accessed on 2 February 2011.

Forestier N, Susser S, Welker MW, Karey U, Zeuzem S, Sarrazin C. Long term follow up of patients previously treated with telaprevir. [abstract 1011] 59th Annual Meeting of the American Association for the Study of Liver DiseasesSan Francisco, California. 31 October -4 November, 2008.

Forns X, García-Retortillo M, Serrano T, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol*. 2003 Sep;39(3):389-96.

Forns X, Marcellin P, Ferenci P, et al. On-treatment response-guided therapy with telaprevir q8h or q12h combined with peginterferon alfa-2a or peginterferon alfa-2b and ribavirin in treatment-naïve genotype 1 hepatitis C (study C208). [abstract 56]. 44th Annual Meeting of the European Association for the Study of the Liver. Copenhagen, Denmark. 22-26 April, 2009.

Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002 Sep 26;347(13):975-82.

Gallegos-Orozco JF, Yosephy A, Noble B, et al. Natural history of post-liver transplantation hepatitis C: A review of factors that may influence its course. *Liver Transpl*. 2009 Dec;15(12):1872-81.

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 Boston, Massachusetts. 30 October – 1 November, 2009.

Gao M, Nettles RE, Belema M, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. *Nature*. 2010 May 6;465(7294):96-100.

Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature*. 2009 Sep 17;461(7262):399-401.

Goulet JL, Fultz SL, McGinnis KA, Justice AC. Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV/HCV-co-infected veterans. *AIDS*. 2005 Oct;19 Suppl 3:S99-105

Grebely J, Knight E, Genoway KA, et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. *Eur J Gastroenterol Hepatol*. 2010 Mar;22(3):270-7.

Greenberg RN. Overview of patient compliance with medication dosing: a literature review. Arch Intern Med. 1990 Sep;150(9):1881-4.
Hall CS, Charlebois ED, Hahn JA, Moss AR, Bangsberg DR. Hepatitis C virus infection in San Francisco's HIV-infected urban poor. *J Gen Intern Med*. 2004 Apr;19(4):357-65.

Harris KA, Arnsten JH, Litwin AH. Successful Integration of Hepatitis C Evaluation and Treatment Services With Methadone Maintenance. *J Addict Med*. 2010 Mar;4(1):20-26.

Hawke RL, Schrieber SJ, Soule TA, et al; SyNCH Trial Group. Silymarin ascending multiple oral dosing phase I study in noncirrhotic patients with chronic hepatitis C. *J Clin Pharmacol*. 2010 Apr;50(4):434-49.

Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin Infect Dis*. 2009 Aug 15;49(4):561-73

Hézode C, Forestier N, Dusheiko G, et al; PROVE2 Study Team. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med*. 2009 Apr 30;360(18):1839-50.

Huang HY, Maguire MG, Miller ER 3rd, Appel LJ. Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplementation trials. *Am J Epidemiol*. 2000 Oct 15;152(8):780-7.

Jacobson IM, Brown RS Jr, McCone J, et al; WIN-R Study Group. Impact of weight-based ribavirin with peginterferon alfa-2b in African Americans with hepatitis C virus genotype 1. *Hepatology*. 2007 Oct;46(4):982-90.

Jacobson IM, McHutchison JG, Dusheiko G, et ; ADVANCE Study Team. Telaprevir inn combination with peginterferon alfa-2a and ribavirin in genotype ! HCV treatment naïve 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.

Jeffers LJ, Cassidy W, Howell CD, Hu S, Reddy KR. Peginterferon alfa-2a (40 kd) and ribavirin for black American patients with chronic HCV genotype 1. Hepatology. 2004 Jun;39(6):1702-8.

Jensen DM, Morgan TR, Marcellin P, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology*. 2006 May;43(5):954-60.

Jensen DM, Wedemeyer H,Herring R Jr, et al. High rates of early viral response, promising safety profile and lack of resistance-related breakthrough in HCV GT 1/4 patients treated with RG7128 plus Peg IFN alfa-2a (40KD)/RBV: Planned week 12 interim analysis from the PROPEL study. [abstract 81] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October -2 November, 2010.

Jover R, Pérez-Serra J, de Vera F, et al. Infection by genotype 5a of HCV in a district of southeast Spain. *Am J Gastroenterol*. 2001 Oct;96(10):3042-3

Khokhar OS, Lewis JH. Reasons why patients infected with chronic hepatitis C virus choose to defer treatment: do they alter their decision with time? *Dig Dis Sci*. 2007 May;52(5):1168-76.

Kieffer TL, Sarrazin C, Miller JS, et al. Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. *Hepatology*. 2007;46: 631–639.

Kim WR, Terrault NA, Pedersen RA, et al. Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. *Gastroenterology*. 2009 Nov;137(5):1680-6.
Kuiken C, Hraber P, Thurmond J, Yusim K. The hepatitis C sequence database in Los Alamos. *Nucleic Acids Res*. 2008 Jan;36 (Database issue):D512-6.

Kukolj G, Benhamou Y, Manns MP et al. BI 201335, a potent HCV NS3 protease inhibitor, in treatment-naïve and-experienced chronic HCV genotype-1 infection: genotypic and phenotypic analysis of the NS3 protease domain. [abstract 954] 44th Annual Meeting of the European Association for the Study of the Liver. Copenhagen, Denmark. 22-26 April, 2009.

Kuller LH, Tracy R, Belloso W, et alINSIGHT SMART Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. 2008 Oct 21;5(10):e203.

Kuntzen T, Timm J, Berical A, et al. Naturally occurring dominant resistance mutations to hepatitis C virus protease and polymerase inhibitors in treatment-naïve patients. *Hepatology*. 2008 Dec;48(6):1769-78.

Kwo PY, Lawitz E, McCone J, et al. HCV-SPRINT-1: Final results SVR 24 NS3 protease inhibitor boceprevir pegIFN alpha-2b/ribavirin HCV 1 treatment naïve patients.[ (abstract 4] 44th Annual Meeting of the European Association for the Study of the Liver. Copenhagen, Denmark. 22-26 April, 2009 (a).

Kwo PY, Lawitz E, McCone J, et al. High sustained virologic response (SVR) in genotype 1 (G1) null responders to peg-interferon alfa-2b (P) plus ribavirin (R) when treated with boceprevir (Boc) combination therapy. [abstract 62] 60th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 30 October – 1 November, 2009(b).

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 Aug 6.

Lagging M, Romero AI, Westin, et al. IP-10 predicts viral response and therapeutic outcome in difficult-to-treat patients with HCV genotype 1 infection. *Hepatology*. 2006 Dec;44(6):1617-25.

Laperche S, Le Marrec N, Girault A, et al. Simultaneous detection of hepatitis C virus (HCV) core antigen and anti-HCV antibodies improves the early detection of HCV infection. *J Clin Microbiol*. 2005 Aug;43(8):3877-83.

Lawiz E, Rodriguez-Torres M, Rustgi V, et al. Safety and efficacy of ANA 598 in combination with pegylated interferon ∂2A plus ribavirin in treatment naïve genotype-1 chronic HCV patients. [abstract 31] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October – 2 November, 2010.

Lechner F, Wong DK, Dunbar PR, et al. Analysis of successful immune responses in persons infected with hepatitis C virus. *J Exp Med*. 2000 May 1;191(9):1499-512.

Legrand-Abravanel F, Henquell C, Le Guillou-Guillemette H, et al. Naturally occurring substitutions conferring resistance to hepatitis C virus polymerase inhibitors in treatment-naive patients infected with genotypes 1-5. *Antivir Ther*. 2009;14(5):723-30.

Lepe R, Layden-Almer JE, Layden TJ, Cotler S. Ethnic differences in the presentation of chronic hepatitis C. *J Viral Hepat*. 2006 Feb;13(2):116-20.

Le Pogam S, Seshaadri A, Kosaka A, et al. Existence of hepatitis C virus NS5B variants naturally resistant to non-nucleoside, but not to nucleoside, polymerase inhibitors among untreated patients. *J Antimicrob Chemother*. 2008 Jun;61(6):1205-16.

Lettmeier B, Mühlberger N, Schwarzer R, et al. Market uptake of new antiviral drugs for the treatment of hepatitis C. *J Hepatol*. 2008 Oct;49(4):528-36.

Levi JE, Takaoka DT, Garrini RH, et al. Three cases of infection with hepatitis C virus genotype 5 among Brazilian hepatitis patients. *J Clin Microbiol*. 2002 Jul;40(7):2645-7.

Lok AS, Gardiner D, Lawitz L, et al. Combination therapy with BMS-790052 and BMS-650032 alone or with PEG/RBV results in undetectable HCV RNA through 12 weeks of therapy in HCV genotype 1 null responders. [abstract LB-8] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October – 2 November, 2010.

Lonardo A, Adinolfi LE, Petta S, Craxì A, Loria P. Hepatitis C and diabetes: the inevitable coincidence? *Expert Rev Anti Infect Ther*. 2009 Apr;7(3):293-308.

López-Labrador FX, Moya A, Gonzàlez-Candelas F. Mapping natural polymorphisms of hepatitis C virus NS3/4A protease and antiviral resistance to inhibitors in worldwide isolates. *Antivir Ther*. 2008;13(4):481-94.

Maieron A, Metz-Gercek S, Hackl F, et al. Chronic hepatitis C in Austria, 1992-2006: genotype distribution and demographic factors. *Euro Surveill*. 2010 Feb 25;15(8):19492.

Mailey B, Buchberg B, Prendergast C, et al. A disease-based comparison of liver transplantation outcomes. *Am Surg*. 2009 Oct;75(10):901-8.

Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001 Sep 22;358(9286):958-65.

Manns MP, Muir A, Adda N, et al. Telaprevir in hepatitis C genotype 1-infected patients with prior non-response, viral breakthrough, or relapse to peginterferon-alpha 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. Copenhagen, Denmark. 22-26 April, 2009.

Marcellin P, Forns X, Goeser T, et al. Virological analysis of patients receiving telaprevir administered q8h or q12h with peginterferon-alfa-2a or -alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C: study C208. [abstract 194] 60th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 30 October -1 November, 2009.

Martin-Carbonero L, Nuñez M, Mariño A, et al. Undetectable hepatitis C virus RNA at week 4 as predictor of sustained virological response in HIV patients with chronic hepatitis C. *AIDS*. 2008 Jan 2;22(1):15-21.

Martín-Santos R, Díez-Quevedo C, Castellví P, et al. De novo depression and anxiety disorders and influence on adherence during peginterferon-alpha-2a and ribavirin treatment in patients with hepatitis C. *Aliment Pharmacol Ther*. 2008 Feb 1;27(3):257-65

Martinot-Peignoux M, Roudot-Thoraval F, Mendel I, et al. Hepatitis C virus genotypes in France: relationship with epidemiology, pathogenicity and response to interferon therapy. The GEMHEP. *J Viral Hepat*. 1999 Nov;6(6):435-43.

Martyak LA, Yeganeh M, Saab S. Hepatitis C and Lymphoproliferative Disorders: From Mixed Cryoglobulinemia to Non-Hodgkin's Lymphoma. *Clin Gastroenterol Hepatol*. 2009 Apr 9.

McCoombs J, Yuan Y, Shin J, Saab S. Chronic hepatitis C infections and the risk of depression and other adverse events. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. [abstract 1895] 29 October – 2 November, 2010.

McHutchison JG, Manns M, Patel K, et al; International Hepatitis Interventional Therapy Group. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology*. 2002 Oct;123(4):1061-9.

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.(a)

McHutchison JG, Lawitz EJ, Shiffman ML, et al; IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009 Aug 6;361(6):580-93.(b)

McHutchison J, Manns MP, Muir AJ, et al; PROVE 3 Study Team. Telaprevir for Previously Treated Chronic HCV Infection. *N Engl J Med*. 2010Apr 8;362(14):1292-303 (a).

McHutchison J, Goodman Z, Patel K, et al; Farglitizar Study Investigators. Farglitazar lacks antifibrotic activity in patients with chronic hepatitis C infection. *Gastroenterology*. 2010 Apr;138(4):1365-73, 1373.e1-2 (b).

Medrano J, Resino S, Vispo E, et al. Hepatitis C virus (HCV) treatment uptake and changes in the prevalence of HCV genotypes in HIV/HCV-coinfected patients. *J Viral Hepat*. 2010 Apr 27.

Mehta SH, Lucas GM, Mirel LB, et al. Limited effectiveness of antiviral treatment for hepatitis C in an urban HIV clinic. *AIDS*. 2006 Nov 28;20(18):2361-9.

Mira JA, López-Cortés LF, Merino D, Arizcorreta-Yarza A, et al; Grupo para el Estudio de las Hepatitis Viricas de la Sociedad Andaluza de Enfermedades Infecciosas. Predictors of severe haematological toxicity secondary to pegylated interferon plus ribavirin treatment in HIV-HCV-coinfected patients. *Antivir Ther*. 2007;12(8):1225-35.

Montaudié H, Passeron T, Cardot-Leccia N, Sebbag N, Lacour JP. Drug Rash with Eosinophilia and Systemic Symptoms due to Telaprevir. *Dermatology*. 2010 Aug 25

Moreno A, Quereda C, Moreno L, et al. High rate of didanosine-related mitochondrial toxicity in HIV/HCV-coinfected patients receiving ribavirin. *Antivir Ther*. 2004 Feb;9(1):133-8.

Moreno C, Deltenre P, Pawlotsky JM, Henrion J, Adler M, Mathurin P. Shortened treatment duration in treatment-naive genotype 1 HCV patients with rapid virological response: A meta-analysis. *J Hepatol*. 2010 Jan;52(1):25-31

Morgan TR, Ghany MG, Kim H-Y, et al. Outcome of sustained virological responders and non-responders in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) Trial. [abstract 115] 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2009). Boston, Massachusetts. 30 October -1 November, 2009.

Morgan TR, Ghany MG, Kim HY, et al; HALT-C Trial Group. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology*. 2010 Sep;52(3):833-44.

Morsica G, Bagaglio S, Uberti-Foppa C, Galli L, Lazzarin A. Detection of hepatitis C mutants with natural resistance to NS3/4A protease inhibitors in HIV/HCV-coinfected individuals treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2009 May 1;51(1):106-8.

Moyle G, Sawyer W, Law M, Amin J, Hill A. Changes in hematologic parameters and efficacy of thymidine analogue-based, highly active antiretroviral therapy: a meta-analysis of six prospective, randomized, comparative studies. *Clin Ther*. 2004 Jan;26(1):92-7.

Muir AJ, Bornstein JD, Killenberg PG; Atlantic Coast Hepatitis Treatment Group. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Engl J Med*. 2004 May 27;350(22):2265-71.

Murray CL, Rice CM. Hepatitis C: An unsuspected drug target. *Nature*. 2010 May 6;465 (7294):42-4.

Nainan OV, Alter MJ, Kruszon-Moran D, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. *Gastroenterology*. 2006 Aug;131(2):478-84

Negro F, Alaei M. Hepatitis C virus and type 2 diabetes. *World J Gastroenterol*. 2009 Apr 7;15(13):1537-47.

Neumann UP, Biermer M, Eurich D, Neuhaus P, Berg T. Successful prevention of hepatitis C virus (HCV) liver graft reinfection by silibinin mono-therapy. *J Hepatol*. 2010 Jun;52(6):951-2.

Núñez-Fernández C, Martín-Carbonero L, Valencia ME, et al Liver complications have reached a plateau as cause of hospital admission and death in HIV patients in Madrid. *AIDS Res Hum Retroviruses*. 2009 Apr;25(4):383-5.

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. January 10, 2011; 1-166. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 3 February 2011.

Payan C, Roudot-Thoraval F, Marcellin P, et al. Changing of hepatitis C virus genotype patterns in France at the beginning of the third millenium: The GEMHEP GenoCII Study. *J Viral Hepat*. 2005 Jul;12(4):405-13.

Perico N, Cattaneo D, Bikbov B, Remuzzi G. Hepatitis C infection and chronic renal diseases. *Clin J Am Soc Nephrol*. 2009 Jan;4(1):207-20

Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol*. 2006 Oct;45(4):529-38.

Peters L; Insight SMART Study Group. Biomarkers of Inflammation and Coagulation and Risk of Non-AIDS Death in HIV/Hepatitis Co-infected Patients in the SMART Study. [ abstract 660] 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, California. 16-19 February, 2010.

Picchio G, Luo D, George S, et al. Discrepansies between definitions of null response to treatment with peginterferon alfa-2A and ribavirin: implications for new HCV drug development [abstract 289] 45th Annual Meeting of the European Association for the Study of the Liver. 14-18 April, 2010. Vienna, Austria.

Picciotto FP, Tritto G, Lanza AG, et al. Sustained virological response to antiviral therapy reduces mortality in HCV reinfection after liver transplantation. *J Hepatol*. 2007 Mar;46(3):459-65.

Poordad F McCone J, Bacon BR, et al; SPRINT-2 Investigators. Boceprevir combined with peginterferon-2b/ribavirin for treatment naïve 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.

Preston FE, Jarvis LM, Makris M, et al. Heterogeneity of hepatitis C virus genotypes in hemophilia: relationship with chronic liver disease. *Blood*. 1995 Mar 1;85(5):1259-62.

Quereda C, Corral I, Moreno A, et al. Effect of treatment with efavirenz on neuropsychiatric adverse events of interferon in HIV/HCV-coinfected patients. *J Acquir Immune Defic Syndr*. 2008 Sep 1;49(1):61-3.

Ragni MV, Moore CG, Soadwa K, et al; THE HHH STUDY GROUP. Impact of HIV on liver fibrosis in men with hepatitis C infection and haemophilia. *Haemophilia*. 2011 Jan;17(1):103-11.

Rallon N, Naggie S, Benito J, et al.) Strong Association of a Single Nucleotide Polymorphism Located Near the Interleukin-28b Gene with Response to Hepatitis C Therapy in HIV/HCV Co-infected Patients. [abstract 165 LB] 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, California. 16-19 February, 2010.

Ramos B, Núñez M, Toro C, et al. Changes in the distribution of hepatitis C virus (HCV) genotypes over time in Spain according to HIV serostatus: implications for HCV therapy in HCV/HIV-coinfected patients. *J Infect*. 2007 Feb;54(2):173-9.
Reau N, Hadziyannis SJ, Messinger D, Fried MW, Jensen DM. Early predictors of anemia in patients with hepatitis C genotype 1 treated with peginterferon alfa-2a (40KD) plus ribavirin. *Am J Gastroenterol*. 2008 Aug;103(8):1981-8.

Rendina M, Castellaneta NM, Fagiuoli S, et al. SVR to antiviral therapy is highly protective against liver-related death in patients with HCV recurrance on the graft after liver transplantation (LT). [abstract 4] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October – 2 November, 2010.

Robaeys G, Van Vlierberghe H, Matheï C, Van Ranst M, Bruckers L, Buntinx F; BASL Steering Committee; Benelux Study Group. Similar compliance and effect of treatment in chronic hepatitis C resulting from intravenous drug use in comparison with other infection causes. *Eur J Gastroenterol Hepatol*. 2006 Feb;18(2):159-66.

Rodriguez-Torres M, Jeffers LJ, et al; Latino Study Group. Peginterferon alfa-2a and ribavirin in Latino and non-Latino whites with hepatitis C. *N Engl J Med*. 2009 Jan 15;360(3):257-67.

Roffi L, Ricci A, Ogliari C, et al. HCV genotypes in Northern Italy: a survey of 1368 histologically proven chronic hepatitis C patients. *J Hepatol*. 1998 Nov;29(5):701-6.

Romano K, Ali A, Schiffer C. Avoiding drug resistance against HCV NS3/4A protease inhibitors. [abstract 17] *Antiviral Therapy*. 2010; 15 Suppl 2: A1-A189

Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. *Gastroenterology*. 2010;138:108–115.

Sarrazin C, Kieffer TL, Bartels D, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. *Gastroenterology*. 2007;132:1767–1777.

Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology*. 2010 Feb;138(2):447-62.

Satapathy SK, Lingisetty CS, Proper S, Chaudhari S, Williams S. Equally poor outcomes to pegylated interferon-based therapy in African Americans and Hispanics with chronic hepatitis C infection. *J Clin Gastroenterol*. 2010 Feb;44(2):140-5.

Schaefer M, Schmidt F, Folwaczny C, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatology*. 2003 Feb;37(2):443-51.

Schiff E, Poordad F, Jacobson I et al. Boceprevir (B) combination therapy in null responders (NR): response dependent on interferon responsiveness. [abstract 104] 43rd meeting of the European Association for the Study of the Liver. 23-27 April 2008. Milan, Italy.

Schneider PJ, Murphy JE, Pedersen CA. Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients. *J Am Pharm Assoc* (2003). 2008 Jan-Feb;48(1):58-63.

Schott P, Hartmann H, Ramadori G. Hepatitis C virus-associated mixed cryoglobulinemia. Clinical manifestations, histopathological changes, mechanisms of cryoprecipitation and options of treatment. *Histol Histopathol*. 2001 Oct;16(4):1275-85.

Seeff LB, Curto TM, Szabo G, et al; HALT-C Trial Group. Herbal product use by persons enrolled in the hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. *Hepatology*. 2008 Feb;47(2):605-12.

Shea DO, Tuite H, Farrell G, et al. Role of rapid virological response in prediction of sustained virological response to Peg-IFN plus ribavirin in HCV / HIV co-infected individuals. *J Viral Hepat*. 2008 Jul;15(7):482-9.

Sherman KE, Fleischer R, Laessig K, Murray J, Tauber W, Birnkrant D; FDA Antiviral Products Advisory Committee. Development of novel agents for the treatment of chronic hepatitis C infection: Summary of the FDA Antiviral Products Advisory Committee recommendations. *Hepatology*. 2007 Dec;46(6):2014-20.

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

Shiffman ML, Morishima C, Dienstag JL, et al; HALT-C Trial Group. Effect of HCV RNA suppression during peginterferon alfa-2a maintenance therapy on clinical outcomes in the HALT-C trial. *Gastroenterology*. 2009 Dec;137(6):1986-94

Sico J, Chang J, Freiberg M, et al; the Veterans Aging Cohort Study. HIV Infection, Hepatitis C Infection, and the Risk of Stroke in the Veterans Aging Cohort Study Virtual Cohort. [abstract 668] 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, California. 16-19 February, 2010.

Silva MB, Andrade TM, Silva LK, et al. Prevalence and genotypes of hepatitis C virus among injecting drug users from Salvador-BA, Brazil. *Mem Inst Oswaldo Cruz*. 2010 May;105(3):299-303.

Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol*. 2010 Mar;8(3):280-8, 288.e1.

Soriano V, Maida I, Núñez M, et al. Long-term follow-up of HIV-infected patients with chronic hepatitis C virus infection treated with interferon-based therapies. *Antivir Ther*. 2004 Dec;9(6):987-92.

Sulkowski MS, Mehta SH, Torbenson MS, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. *AIDS*. 2007 Oct 18;21(16):2209-16.

Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. *Hepatology*. 2009 Dec;50(6):1709-18.(a)

Susser S, Forestier N, Welker MW, et al. Detection of resistant variants in the hepatitis C virus NS3 protease gene by clonal sequencing at long-term follow-up in patients treated with boceprevir. [abstract 12] 44th Annual Meeting of the European Association for the Study of the Liver. 22-26 April, 2009. Copenhagen, Denmark.(b)

Sylvestre DL, Clements BJ. Adherence to hepatitis C treatment in recovering heroin users maintained on methadone. *Eur J Gastroenterol Hepatol*. 2007 Sep;19(9):741-7.

Tauber W; FDA. Food and Drug Administration Antiviral Drugs Advisory Committee. Pegasys® Copegus®, Hoffmann-LaRoche,Indications and Usage, FDA. November 14, 2002. Available at: http://www.fda.gov/ohrms/dockets/ac/2/slides/3909S1.htm (Accessed 2 February 2011).

Terrault NA, Berenguer M. Treating hepatitis C infection in liver transplant recipients. Liver Transpl. 2006 Aug;12(8):1192-204.
Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS*. 2008 Oct 1;22(15):1979-91.

Thimme R, Oldach D, Chang KM, et al. Determinants of viral clearance and persistence during acute hepatitis C virus infection. *J Exp Med*. 2001 Nov 19;194(10):1395-406.

Thomas DL, Thio CL, Martin MP,et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009 Oct 8;461(7265):798-801.

Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. *Am J Transplant*. 2010 Apr;10(4 Pt 2):1003-19

Tuaillon E Mondain AM, Meroueh F, et al. Dried blood spot for hepatitis C virus serology and molecular testing. *Hepatology*. 2010 Mar;51(3):752-8.

Tuke PW, Grant PR, Waite J, Kitchen AD, Eglin RP, Tedder RS. Hepatitis C virus window-phase infections: closing the window on hepatitis C virus. *Transfusion*. 2008 Apr;48(4):594-600.

Verma S, Bonacini M, Govindarajan S, Kanel G, Lindsay KL, Redeker A. More advanced hepatic fibrosis in hispanics with chronic hepatitis C infection: role of patient demographics, hepatic necroinflammation, and steatosis. Am J Gastroenterol. 2006 Aug;101(8):1817-23.

Verbeeck J, Stanley MJ, Shieh J, et al. Evaluation of Versant hepatitis C virus genotype assay (LiPA) 2.0. *J Clin Microbiol*. 2008 Jun;46(6):1901-6.

Vogel M, Rockstroh JK. Treatment of acute hepatitis C in HIV infection. J Antimicrob Chemother. 2010 Jan;65(1):4-9.
Volk ML, Tocco R, Saini S, Lok AS. Public health impact of antiviral therapy for hepatitis C in the United States. *Hepatology*. 2009 Dec;50(6):1750-5.

Wagoner J, Negash A, Kane OJ, et al. Multiple effects of silymarin on the hepatitis C virus lifecycle. Hepatology. 2010 Jun;51(6):1912-21.
Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006 Aug 14-28;166(15):1632-41.

Wiegand J, Buggisch P, Boecher W, et al;; German HEP-NET Acute HCV Study Group. Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatology*. 2006 Feb;43(2):250-6.

Winters MA, Chary A, Eison R, Asmuth D, Holodniy M. Impact of highly active antiretroviral therapy on hepatitis C virus protease quasispecies diversity in HIV co-infected patients. *J Med Virol*. 2010 May;82(5):791-8.

World Health Organization. Initiative for Vaccine Research (IVR). Viral Cancers, Hepatitis C. 2009. Available at: http://www.who.int/vaccine_research/diseases/viral_cancers/en/index2.html (Accessed 3 February 2011).

World Hepatitis Alliance. *Viral Hepatitis: Global Policy*. Available at: http://www.worldhepatitisalliance.org/Policy/2010PolicyReport.aspx (Accessed on 3 February 2011).

Yu JW, Wang GQ, Sun LJ, Li XG, Li SC. Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. *J Gastroenterol Hepatol*. 2007 Jun;22(6):832-6.

Yu ML, Dai CY, Huang JF et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. *Hepatology*. 2008 Jun;47(6):1884-93.

Zeuzem S, Asselah T, Angus PW, et al. Strong antiviral activity and safety of IFN-sparing treatment with the protease inhibitor BI 201335, the HCV polymerase inhibitor BI 207127 and ribavirin in patients with chronic hepatitis C. [abstract LB-7] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October – 2 November, 2010 (a).

Zeuzem S, Buggisch P, Agarwal K, et al. Dual, triple and quadruple combination treatment with a protease inhibitor (GS-9256) and a polymerase inhibitor (GS-9190) alone and in combination with ribavirin (RBV) or Peg/IFN/RBV for up to 28 days in treatment naïve genotype 1 HCV subjects. [abstract Oral LB-1] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October – 2 November, 2010 (b).

Zeuzem S, Sulkowski MS, Zoulim F, et al. Long-term follow-up of patients with chronic hepatitis C treated with telaprevir in combination with peginterferon alfa-2a and ribavirin: Interim analysis of the EXTEND study. [abstract 227] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. 29 October – 2 November, 2010.