

# Hepatitis C: New Treatments in the Pipeline

By Tracy Swan  
Treatment Action Group  
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BI 12202 • Boceprevir (SCH 503034)  
• Farglitazar • GI- 5005 • GS 9190  
ICV E1/E2 Vaccine • IC41 • IMO-2125  
on • MitoQ • MK70009 • MX-3253  
a Interferon • Peg-Interferon Lambda  
491390 (IDN-6556) • R1626 • R7128  
40 • TMC435350 • VCH-759 • VX-500

## About Treatment Action Group

Treatment Action Group (TAG) is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people living with HIV receive life saving treatment, care, and information.

We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policymakers to end AIDS.

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**Dedicated to:** Phyllis Beck  
and

Narelle Ellendon, Shari Foster, Ronni Marks, Sharon Phillips, Lorren Sandt, Sue Simon and Andi Thomas

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## Foreword

I became an AIDS activist in 1986, when my husband was diagnosed with AIDS. He died from AIDS-related complications in 1987. While I'm very grateful I am not HIV-positive, last year I was diagnosed with hepatitis C. Just because I don't now present as a party girl doesn't mean I don't have such risk factors in my background. In fact, the insidious hepatitis C virus has apparently been lounging in my liver for many years.

I am also a cancer chemotherapy and radiation survivor who is older and frailer than in days gone by. I know that I could never tolerate 48 weeks of pegylated interferon and ribavirin. Moreover, like most of us, I cannot afford to be unemployed for any great length of time. Many HCV patients are in my age range and have other health issues. We need more effective, better-tolerated, and more easily administered treatments.

By 2007, we thought we had finally reached a turning point; we believed we had found a new paradigm for HCV treatment. If only that were the case. Although effective drugs are on the horizon, interferon and ribavirin are still the mainstay of HCV treatment, and the community is rife with rumors that toxicities from some initially promising new drugs may outweigh their benefits.

Where do we go from here? The issues are both numerous and complex. Some patients are in a position to wait for new drugs, but many others are not. Many patients cannot tolerate the current standard of care. Those with poor prognostic factors, such as people with HCV genotype 1 and a high viral load; HIV-positive people; African Americans; and people who have already developed serious liver damage are in big trouble, since they are less likely to respond to currently marketed HCV treatment.

What about treatment-experienced patients who have already tried standard interferon, with or without ribavirin? While some of these patients do respond to pegylated interferon plus ribavirin, the data on re-treatment response rates are discouraging. There are currently no approved treatments for people who do not respond to pegylated interferon and ribavirin. Therapeutic vaccines for HCV, or improvements in interferon-based therapy, may offer some hope in the near future.

I believe that AIDS treatment activists have moved the field of HIV research forward swiftly, dramatically, and in a way that nothing else has. We can do the same for hepatitis C. We know that we need combinations of small molecules such as protease and polymerase inhibitors to replace interferon and/or ribavirin. Combination regimens targeting different areas of the HCV life cycle, with different mechanisms of action, are necessary to forestall resistance and effectively combat HCV. Until this is possible, we can at least hope that new drugs will boost response rates, and decrease the amount of time people must spend on these poorly tolerated treatments.

HCV researchers would do well to reflect on, and apply scientific and pragmatic lessons from, HIV research. As an advocate for people with HIV, I can't even utter the word *resistance* without acknowledging the harm done to so many people by poorly designed clinical trials,

and from non-strategic prescribing of HIV antiviral therapy over the years. We will be working to remedy the misuse of effective treatment for years to come. We sincerely hope that HCV researchers and clinicians can learn from and avoid such mistakes.

We can also learn from the successes in HIV research and treatment. The development of more effective treatments for HIV, including once-daily and one-pill regimens, speaks volumes about the resounding success of well-funded modern medical research, and the contribution of AIDS activists. We have brought a fresh perspective to the field by speaking out at conferences and meetings without fear of losing grant funding or tenure as a result of our criticisms. We have worked successfully to ensure that crucial funding is available to support successful research efforts. In the United States, we continue to work as federal watchdogs by helping to draft FDA accelerated-approval regulations and new drug-safety legislation. Activists continue to participate in the design and oversight of clinical trials, and to disseminate information directly to affected communities.

As advocates and activists, we clearly understand the ever-present tension between getting a drug approved and studying the most strategic use of new drugs. But no one benefits from badly designed studies that rush a drug to market, particularly those that exclude African Americans, HIV-positive people, prior drug users, or other patient groups among whom HCV is common—and the unmet medical need is great. Such studies are impractical, counterproductive, and unacceptable, and will not be tolerated by the patient community or FDA. Remember, consumers are included in FDA Advisory Panels.

Companies need to be as forthcoming as possible with the patient and provider communities about incidence and management of long- and short-term side effects and other tolerability issues. Companies would do better to share such information honestly, and sooner rather than later. It's not as if the facts don't eventually surface. Building trust throughout the drug development process can only benefit sponsors, especially since FDA is now armed with new drug safety laws to more effectively address long-term patient safety issues.

Researchers and clinicians would also do well to remember the heavy toll interferon and ribavirin take on patients. Implying that patients are at fault for not being able to adhere to such a difficult regimen is misguided. Referring to such people as "noncompliant" is insensitive and insulting. Instead, companies should work with researchers and the community to provide reasonable support services for patients undergoing treatment with these difficult regimens.

Congress must also allocate new monies to assist patients, instead of pitting disease groups against each other to argue over insufficient federal funds. Medicine, especially medical research, is inextricably entwined with politics in the good old USA. Getting new money from Congress for what is essentially an unpopular, and often disenfranchised, population will undoubtedly be a daunting task. Our economy and our treasury leave a lot to be desired at this juncture. Hopefully, prioritization that puts people and life before war and death will be upon us after November 2008.

“Thank you” hardly reflects the appreciation I feel towards the Treatment Action Group (TAG), and my friend and colleague, Tracy Swan, the “Countess of Coinfection,” for their work with other activists, members of the medical and research communities, drug companies, and regulatory agencies. My long career as an AIDS activist convinces me and if we work together, more effective, better-tolerated regimens will be available much more quickly. I wish you sweeping and swift future success.

Lynda Dee  
Co-founder of AIDS Action Baltimore.



## Introduction

*Preventing new infections will not impact the predicted wave of morbidity and mortality from persons already infected.*

*While better and more affordable treatments are eagerly anticipated, much can be accomplished in the interim.*

*Affected countries must face the dilemmas at hand and give careful consideration to the array of available options for addressing and minimizing the coming wave of HCV-related liver disease.*

*Current strategies to reduce the long-term sequelae of chronic HCV infection include identifying infected persons by testing those at high risk and offering counseling, medical evaluation and treatment.*

—J.F. Perz and M.J. Alter  
*Journal of Hepatology*

Hepatitis C virus (HCV) is a serious global health problem. According to the World Health Organization (WHO), which describes HCV as a “viral time bomb,” 130 million people have chronic hepatitis C, and 3 to 4 million more become infected each year (WHO 2007). If untreated, or unresponsive to treatment, chronic HCV leads to cirrhosis in 20–30% of people. Each year, ~4% of people with hepatitis C-associated cirrhosis develop liver cancer, and ~6% will experience liver failure (Di Bisceglie 2000). WHO estimates that up to 75% of liver cancer and ~65% of liver transplants occurring in the developed world are attributable to chronic HCV infection (WHO 2007).

The current standard of care for HCV, pegylated interferon and ribavirin, is not effective for approximately half of those who undergo it, and the side effects are often debilitating.

The need for new therapies for hepatitis C virus is more urgent than ever, particularly for a growing population of treatment-experienced people with serious liver damage. Results from HALT-C and SLAM-C—two interferon maintenance trials for people with advanced liver damage—were an unexpected disappointment. Both reported that maintenance therapy did not reduce fibrosis progression, hepatic decompensation, or liver-related mortality, leaving no stopgap until new drugs are available (Di Bisceglie 2007; Sherman 2008). Without advances in, and broader access to, HCV treatment, liver-related mortality is expected to rise sharply in the coming years (Davis 2003).

Better HCV treatment is critical for the estimated 4 to 5 million HIV/HCV-coinfected people (Alter 2006). HIV increases the risk for and rate of hepatitis C progression. In fact, end-stage liver disease is now the leading cause of non-AIDS-related death among HIV-positive people in areas where antiretroviral therapy is available (Weber 2006).

HCV treatment is far less effective for HIV/HCV-coinfected people (see Table 1. SVR from Clinical Trials by HCV Genotype and HIV Status [Treatment with PEG-IFN plus ribavirin], below). HIV/HCV-coinfected people tend to have more severe—often treatment-limiting—side effects from HCV treatment, and many are not considered eligible for treatment.

It is incredibly ironic that we have dramatically altered the prognosis for HIV—a currently incurable disease—only to see coinfected people dying from complications of hepatitis C, a disease that we can cure.

Sponsors need to initiate studies of novel HCV drugs in coinfected people as soon as it is safe to do so, preferably in parallel with phase III. Drug-drug interaction studies with antiretroviral agents and other commonly used medications should be performed as early in development as possible to expedite these important trials.

**Table 1. SVR From Clinical Trials by HCV Genotype and HIV Status (Treatment with PEG-IFN plus ribavirin)**

Population	SVR, Overall	SVR, Genotype 1	SVR, Genotype 2&3
HIV/HCV coinfected	27% – 44%	14% – 38%	53% – 73%
HCV monoinfected	56% – 61%	42% – 44%	70% – 82%

Sources:

Carrat F, Bani-Sadr F, Pol S, et al. ANRS HCO2 RIBAVIC Study Team. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA*. 2004 Dec 15;292(23):2839–48.

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## SETBACKS

2007 was a year of many setbacks. The development of several candidates was halted due to toxicity, insufficient efficacy, and/or financial concerns: NM 283 and HCV-796 (polymerase inhibitor candidates from Idenix and Wyeth/Viropharma); ACH-806 /GS 9132 (an HCV protease inhibitor co-developed by Achillion/Gilead); AVI-4065 (an antisense drug from AVI BioPharma); Actilon (a TLR9 antagonist from Coley pharmaceuticals); and VGX-410 C (an oral IRES inhibitor from VGX Pharmaceuticals). Development of MAXY-alpha (a novel interferon formulation co-developed by Roche and Maxygen) was put on hold and is unlikely to resume. XLT Pharmaceuticals suspended development of XTL-2125, a polymerase inhibitor, and XTL 6865, a monoclonal antibody.

Doses of promising candidates have been modified due to safety issues. Gilead is going with a lower dose of GS 9190, an HCV polymerase inhibitor. During the phase III study of Albuferon (a longer-lasting formulation of interferon being developed by Human Genome Sciences and Novartis), a Data Safety Monitoring Board (DSMB) discontinued the highest dosing arm, due to pulmonary adverse events.

A drastic shift in the HCV treatment paradigm will not occur for several years, since interferon-free regimens are years away, and ribavirin is still a necessary component of HCV treatment. Recent research has underscored its value for preventing viral breakthrough and lowering relapse rates. Given emerging concerns with new therapies—toxicity, drug-drug interactions, resistance, and adherence—it is especially disappointing to remain saddled with the current standard of care.

HCV treatment uptake will not increase significantly until combinations of more effective, less toxic, more affordable drugs are available, particularly for people who are unlikely to respond to, or unable to tolerate, the current standard of care. According to Data Monitor, in 2006, sales of pegylated interferon and ribavirin—the current standard of care for HCV—reached \$2.5 billion in the U.S. and Europe; but sales are projected to increase by only \$1.5 billion by 2010, reflecting the limitations of the current treatment. Better HCV drugs will be a jackpot for the pharmaceutical industry.

## **PROGRESS**

The efficacy of HCV treatment improved with the advent of pegylated interferon-based regimens, and there has been additional progress since then. A steady parade of new agents is moving forward into preclinical and clinical development; researchers toil in state-of-the-art laboratories, developing new drugs, attempting to identify correlates of spontaneous viral clearance and response to HCV treatment, and characterizing resistance to new HCV antiviral drugs. Activists are working with regulators, researchers, and industry to develop guidance for swift, strategic, and inclusive drug development.

More effective, shorter-course HCV treatment is on the horizon. The pipeline is full of second-generation candidates and new approaches, such as RNA interference, to thwart HCV replication. Promising results have been reported from phase II studies of Vertex's HCV protease inhibitor, telaprevir, and from Romark's phase II study of nitazoxanide, an approved anti-protozoal agent. Data are flowing in from phase I studies of protease and polymerase inhibitors. In the future, coformulated versions of these oral drugs may be possible.

## LESSONS LEARNED

The remarkable successes, complexities, and challenges in HIV research and clinical care offer valuable lessons for HCV drug development, care, and treatment.

### Research Issues: Trial Design and Study Populations

- Trials need to be designed to identify therapeutic strategies, as well as to gain approval for a single agent.
- As with HIV, a combination of drugs, targeting different steps in the HCV life cycle, is needed to ward off resistance. Cross-company collaboration on multi-agent trials (involving both approved and experimental drugs) is needed to advance the field. Regulators can facilitate these collaborations by developing regulatory guidance for multi-experimental agent trials.
- Sponsors must study safety, efficacy, and tolerability of new HCV treatments and treatment regimens in clinically relevant populations prior to approval. This means exploring new therapies in populations that are hard to treat and may have urgent, unmet needs, such as: HIV/HCV-coinfected people; African Americans; people with genotype 1 and/or high baseline HCV RNA; transplant candidates and recipients; people with advanced liver damage; current and former drug users; and the rapidly growing population of treatment-experienced people.
- There are practical and financial reasons for sponsors to conduct registration trials in “real-life” populations. From a regulatory perspective, “... it is important that a good sampling of the patients who will receive the drug be part of registration trials” (Dr. Debra Birnkrant, FDA, 2006). More inclusive trials will enroll more quickly and are more feasible, because the number of cherry-picked, otherwise completely healthy, treatment-naïve patients available to participate in HCV treatment trials is dwindling. Securing a broader indication facilitates drug sales, since insurers have begun to limit access to off-label use of drugs, and it is likely that restrictions will increase in the future.
- There are specific issues involved in designing re-treatment trials for people who did not respond to pegylated interferon and ribavirin.
- Re-treating these non-responders with an identical regimen has yielded SVR rates of ~3% (Rustgi 2008). Future trials in this group of non-responders should offer more than one novel agent, preferably in a factorial design when possible. Until combinations of drugs are available, these re-treatment trials need to incorporate successful re-treatment strategies into their design—especially into the control arm—so that participants have the best possible chance to achieve sustained virological response (SVR; see Terms for Response to HCV Treatment, page 34; see also Table 2, page 11. Re-treatment Trials in Non-Responders to at Least 12 Weeks of PEG-IFN and Ribavirin: Strategies and SVR). These strategies may involve extending the duration of treatment, or using a different formulation of interferon, or a higher dose of ribavirin.

**Table 2. Re-treatment Trials in Non-Responders to at Least 12 Weeks of PEG-IFN and Ribavirin: Strategies and SVR**

Treatment Strategy	SVR	Comments
<b>REPEAT ~90% HCV Genotype 1</b>		
Double Dose Induction, Standard Duration 360µg PEG-IFN for 12 weeks, followed by 180µg PEG-IFN + RBV for 36 weeks	11/156 (7%)	Induction dosing did not make a significant difference in SVR 14/156 (9%) experienced serious adverse events 7/156 (4%) discontinued for safety
Double Dose Induction, Extended Duration 360µg PEG-IFN for 12 weeks, followed by 180µg PEG-IFN + RBV for 60 weeks	52/317 (16%)	Extending duration of treatment increased SVR, lowered relapse rate 33/317 (10%) experienced serious adverse events 37/317 (12%) discontinued for safety
Standard Dose, Standard Duration 180µg PEG-IFN + RBV for 48 weeks	27/313 (9%)	33/313 (11%) experienced serious adverse events 20/313 (6%) discontinued for safety
Standard Dose, Extended Duration 180µg PEG-IFN + RBV for 72 weeks	22/156 (14%)	28/156 (18%) experienced serious adverse events 18/156 (12%) discontinued for safety
<b>DIRECT (Daily Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy) ~95% HCV genotype 1</b>		
Control: no treatment after lead-in	SVR 12 = 0%	Participants in the control arm eligible for roll-over study
Interferon alfacon 9µg/day + RBV for 48 weeks	SVR 12 = 5.3%	14% discontinued for adverse events
Interferon alfacon 15µg/day + RBV for 48 weeks	SVR 12 = 9.5%	14% discontinued for adverse events
<b>The German Consensus Interferon Multicenter Study (Interim Results) 96% HCV genotype 1</b>		
<u>Low-dose induction 9/9</u> Interferon alfacon 9µg/day for 16 weeks, followed by Interferon alfacon 9µg/day + weight-based RBV for 32-56 weeks	13%	SVR differed by original regimen: 13% for PEG-alfa 2b vs. 19% for PEG alfa-2a
<u>High-dose induction 27/18/9</u> Interferon alfacon 27µg/day for 4 weeks, followed by Interferon alfacon 18µg/day for 12 weeks, followed by Interferon alfacon 9µg/day + weight-based RBV for 32-56 weeks	19%	SVR differed by original regimen: 19% for PEG-alfa 2b vs. 27% for PEG alfa-2a Although treatment discontinuation did not differ by treatment arm, the high-dose induction was less tolerable

Sources:

Jensen DM, Freilich B, Andreone P, et al. (abstract LB4) Pegylated interferon alfa-2a (40KD) plus ribavirin (RBV) in prior non-responders to pegylated interferon alfa-2b (12KD)/RBV: final efficacy and safety outcomes of the REPEAT study. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 2-6, 2007.

Bacon B, Regev A, Ghalib RH, et al. (abstract 168) The DIRECT trial (Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy): treatment of non-responders to previous pegylated interferon plus ribavirin: sustained virologic response data. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 2-6, 2007.

## Care and Treatment Issues: Resistance/Adherence, Appreciating Toxicity, Multidisciplinary Systems, and HCV Treatment Guidelines

- Resistance to HCV protease and polymerase inhibitors can develop rapidly. The first generation of HCV protease inhibitors to reach phase II must be taken three times a day, every eight hours—a dosing schedule associated with poor adherence (Claxton 2001).
- Liver specialists may be unaccustomed to providing adherence support. Methods that are proven to promote adherence—such as patient support and education, and pillboxes—should be incorporated into clinical trials and clinical practice (Peterson 2007; Rueda 2006).
- Liver specialists will need information on the importance and interpretation of resistance testing to optimize HCV treatment outcomes.
- When targeting a virus, the patient often seems to get in the way. It is a mistake to underestimate the importance of tolerability, which is sometimes overlooked by eager researchers in their quest to cure hepatitis C.
- In the United States, the majority of people with chronic hepatitis C are 40 to 59 years old. Many have other chronic health problems, family responsibilities, and demanding jobs that make it difficult or impossible for them to tolerate the current standard of care, resulting in low rates of treatment uptake and completion.
- Therapeutic advances must be accompanied by health-care delivery systems suited to the needs of multiply diagnosed persons. These systems need to be created now to meet current needs and in anticipation of future improvements in HCV treatment.
- It is likely that the standard of care for HCV will become somewhat of a moving target in the coming years. Convening an expert, cross-disciplinary panel to develop and update HCV treatment guidelines will optimize treatment and avert therapeutic chaos.

## Community Involvement

- Since the late 1980s, when they demanded to be treated as partners in HIV research, people with HIV/AIDS and treatment activists have become vital participants in HIV drug development. They serve on scientific peer-review committees, protocol teams, regulatory advisory committees, and treatment guidelines panels. Activists work with sponsors of public and private research, and participate in the design and oversight of clinical trials.

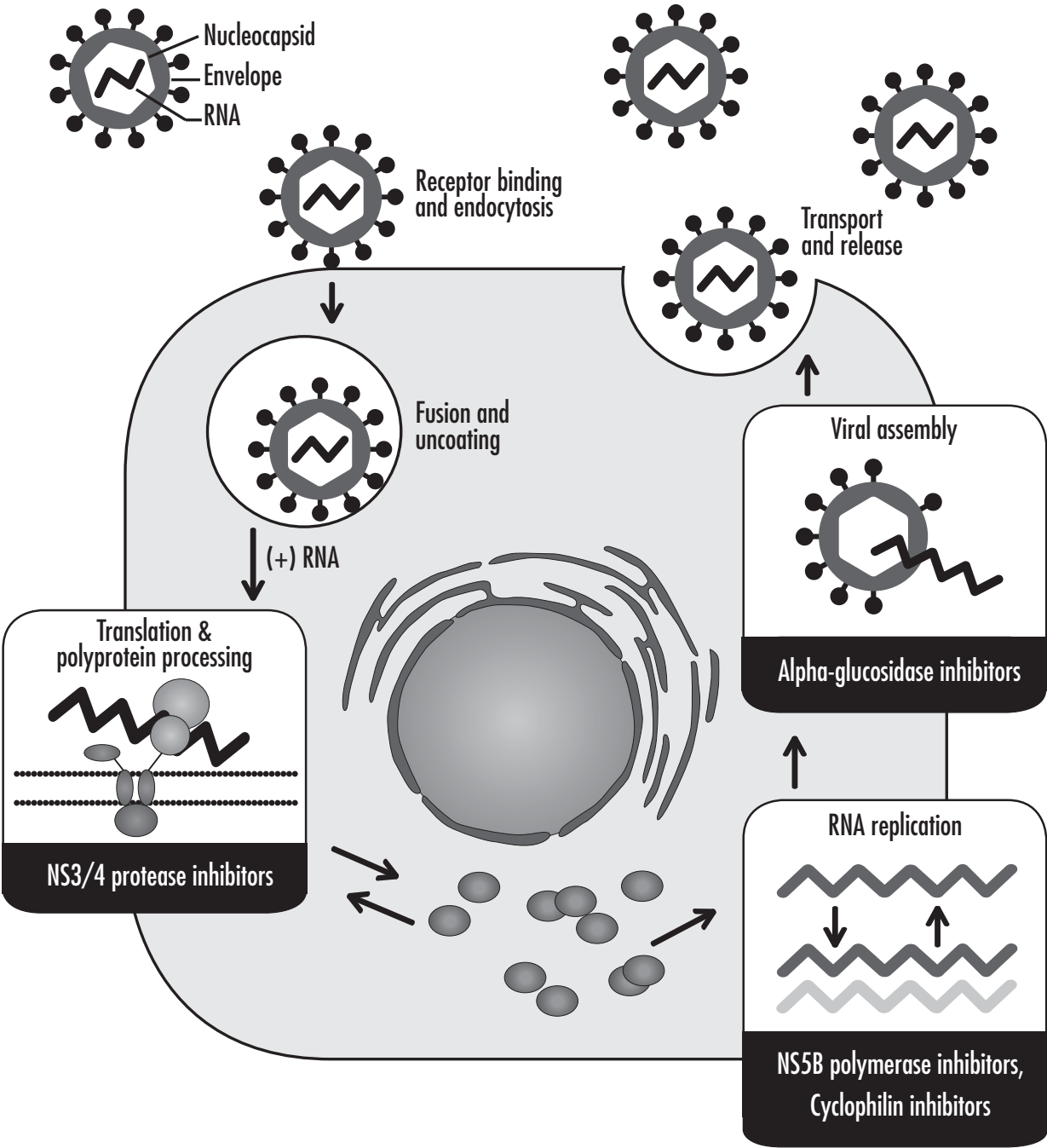
- HCV researchers have much to gain by working more closely with activists and community members. Many bring an often-overlooked, practical perspective to areas ranging from drug development to delivery of care and treatment. Continuing to exclude members of the HCV community from contributing as fully respected partners in hepatitis C research is counterproductive and shortsighted.

## **ACCESS**

Our challenge is to ensure that advances in HCV treatment are available to all who need them, since a majority of people with hepatitis C live in poverty. Hepatitis C is a disease that reflects and magnifies global social and economic inequality. Limited—or the complete lack of—access to HCV prevention, care, and treatment render these virtually useless to millions of people with chronic hepatitis C. We can decrease HCV-related morbidity and mortality if we:

- Ensure adequate coverage of additional costs associated with HCV care and treatment, such as diagnostic testing and other lab work; nursing and clinic staff time; management of side effects; and mental health care;
- Anticipate future costs, such as resistance testing and adherence support services, and provide funding; and
- Work to develop a reasonable, high-volume, low-profit framework for global pricing of HCV drugs and diagnostics.

Figure 1. Targets for HCV Drugs



## Oral Antivirals: HCV Protease and Polymerase Inhibitors

The NS3-4A serine protease enzyme and the NS5B RNA-dependent RNA polymerase enzyme are primary targets for oral antiviral agents, since both enzymes are essential for HCV replication. Unfortunately, HCV's high replication rate—billions of copies per day—leads to drug resistance. In fact, mutations in HCV's protease and polymerase domains have already been characterized, both *in vitro* and *in vivo* (Le Pogam 2006; Zhou 2008).

The consequences of acquiring HCV drug resistance are currently unknown; it may be a transient phenomenon since HCV does not integrate into the host cell's genome. But it is possible that mutations may confer resistance to an agent—or an entire class of agents. Drug-resistant HCV may be less fit, but a lower replication capacity will be a scant consolation for people who have acquired a treatment-resistant virus (Mo 2005; Zhou 2007). Studies of people who have developed resistance to HCV antivirals should be performed in order to fully understand the clinical implications of HCV drug resistance.

As with HIV, hepatitis C treatment requires a combination of drugs that target different steps in the replication cycle. Sponsors will need to collaborate on multi-agent trials to identify and optimize treatment strategies. Unfortunately, we must wait until there are enough drugs at similar stages of development, while pushing to facilitate these studies through dialogues with industry, researchers, and regulators.

### HCV Protease Inhibitors

BILN-2061, an HCV protease inhibitor from Boehringer Ingelheim, was the first of its class. Although BILN-2061 was discontinued due to cardiotoxicity in animals, proof of concept was established (Lamarre 2003). Since then, there have been high hopes for HCV protease inhibitors, and several are in clinical development. So far, all have been studied in people with HCV genotype 1. Telaprevir, an HCV protease inhibitor being co-developed by Vertex and Tibotec, is also being studied in people with genotypes 2, 3, and 4 in trials outside of the U.S.

#### HCV Protease Inhibitors (oral)

Product	Manufacturer	Status
BI 12202*	Boehringer Ingelheim	Phase I
Boceprevir (SCH 503034)	Schering Plough	Phase II
ITMN-191 (R7227)	Intermune/Roche	Phase Ib
MK-7009	Merck/Isis	Phase Ib
Telaprevir (VX-950)	Vertex	Phase III
TMC 435350	Medivir/Tibotec	Phase II
VX-500	Vertex	Phase Ia

\* Information not confirmed by sponsor

- **BI 12202**

Boehringer Ingelheim has not released information about their HCV protease inhibitor candidate.

- **Boceprevir**

Schering has conducted a pair of phase II studies of boceprevir, their HCV protease inhibitor. Their dose-finding study assessed safety and efficacy of 100, 200, and 400 mg/TID (three times daily), plus pegylated interferon, with or without ribavirin, in non-responders with HCV genotype 1. African Americans were initially excluded from this study, until an additional, higher-dose arm (boceprevir 800 mg/TID) was added. The company permitted 15 African Americans to enroll in the higher-dose arm, due in part to community outrage.

The protocol was subsequently amended, when concerns about lack of response in the low-dose arms led the Data and Safety Monitoring Board (DSMB) to recommend that all virological responders be given the 800 mg dose plus ribavirin.

Schering is also studying safety and efficacy of boceprevir plus pegylated interferon and ribavirin in treatment-naïve people with HCV genotype 1 in an ongoing trial. HCV SPRINT-1 (Serine Protease Inhibitor Therapy-1) is a seven-arm study, evaluating 800 mg of boceprevir TID. Notably, participants in two arms of HCV SPRINT-1 are receiving a lower-than-usual dose of ribavirin (400–1,000 mg/day, rather than 800–1,400 mg/day according to weight).

In October 2007, Schering issued a press release announcing the top-line results of their non-responder study, and interim results from HCV SPRINT-1, the treatment-naïve trial. More details are expected at the European Association for the Study of the Liver (EASL) meeting in April 2008. Until then, a hodgepodge of regimens, doses, and treatment durations make it difficult to interpret the results, which ranged from 7% to 14% SVR in the boceprevir arms, versus 2% of those in the control arm (who were re-treated with pegylated interferon and ribavirin). Headache, nausea, fatigue, and anemia were the most commonly reported adverse events.

Interim results from HCV SPRINT-1, the treatment-naïve study, are promising. The early virological response rates (EVR; see Terms for Response to HCV Treatment, page 34) ranged from 54% to 79% in the boceprevir arms, vs. 34% in the control arm (pegylated interferon plus ribavirin). Adverse events were the same as those in the non-responders study: fatigue, headache, nausea, and anemia. Discontinuation rates were higher in the boceprevir arms, ranging from 8% to 12%, versus 5% in the control arm.

Schering is planning to launch phase III studies in the near future.

- **ITMN-191**

Intermune and Roche are co-developing ITMN-191 (also referred to as R7227), an HCV protease inhibitor. Their ongoing phase Ib study is evaluating safety, pharmacokinetics, and activity of ITMN-191 in people with HCV genotype 1. The drug will be studied in treatment-

naïve people initially, then in the treatment-experienced. A 14-day trial, combining ITMN-191 with pegylated interferon and ribavirin, is planned for the second quarter of 2008.

- **MK-7009**

Merck is conducting a safety and efficacy study with a range of doses of MK-7009 in 145 people with HCV genotype 1, both treatment-naïve and treatment-experienced. Study completion is expected by November 2008.

- **Telaprevir (VX-950)**

Vertex has studied different durations of treatment with their HCV protease inhibitor, telaprevir, plus pegylated interferon, with or without ribavirin. Given the nasty side-effects profile of the background regimen, Vertex is hoping that adding telaprevir will shorten the course of treatment and increase efficacy, to counterbalance additional toxicity. The cornerstone of their development program has been to use telaprevir as briefly as possible, and to eliminate or abbreviate the subsequent course of pegylated interferon and ribavirin.

There have been disturbing reports of a telaprevir-associated rash, severe enough in some cases to warrant hospitalization and/or discontinuation of treatment. Hopefully, the company will issue guidance on rash management as they roll out their phase III program, which is slated to begin in March 2008.

PROVE 1, 2, and 3, Vertex’s phase II trials, are fully enrolled. PROVE 1 and 2 are studying different durations of telaprevir-based treatment vs. the standard of care in treatment-naïve persons with HCV genotype 1. PROVE 3 is studying 24 to 48 weeks of telaprevir-based regimens vs. the standard of care in treatment-experienced persons with HCV genotype 1.

Interim results from PROVE 1 and PROVE 2 were announced in November 2007 at the meeting of the American Association for the Study of Liver Diseases (AASLD).

## PROVE 1

Figure 2. PROVE 1 Study Design (United States)

		Week 12	Week 24	Week 36	Week 48	Week 72
Arm A (N=20)	TVR+PEG+RBV	Follow Up				
Arm B (N=80)	TVR+PEG+RBV	PEG+RBV	Follow Up			
Arm C (N=80)	TVR+PEG+RBV	PEG+RBV			Follow Up	
Arm D (N=80)	PEG+RBV				Follow Up	

In PROVE 1, the rapid virological response (RVR; see Terms for Response to HCV Treatment, page 34) guided duration of treatment; therapy was stopped at week 12 or week 24 only for those participants with an RVR. Overall, 18% of study participants in the telaprevir arms

discontinued treatment, 13% for adverse events (telaprevir-associated rash was the most common reason) versus an overall rate of 3% in the control arm (2% for adverse events). Itchy skin, rash, gastrointestinal problems, and anemia occurred more frequently among participants who received telaprevir (Jacobson 2007).

**Table 3. PROVE 1: Interim Results by Intent-To-Treat Analysis**

Regimen and N	RVR undetectable* HCV RNA at week 4; data pooled from all TPV arms	Interim results
Arm A (N=17) TVR + PEG-IFN + RBV for 12 weeks	79%	SVR: 35%
Arm B (N=79) TVR + PEG-IFN + RBV 12 weeks, followed by PEG-IFN + RBV for 12 weeks	79%	SVR: 61%
Arm C (N=79) TVR + PEG-IFN + RBV for 12 weeks, followed by PEG-IFN + RBV for 36 weeks	79%	65% undetectable at end of treatment; SVR not yet available
Arm D - Control (N=75) PEG-IFN + RBV + TVR placebo for 48 weeks	11%	45% undetectable at end of treatment; SVR not yet available

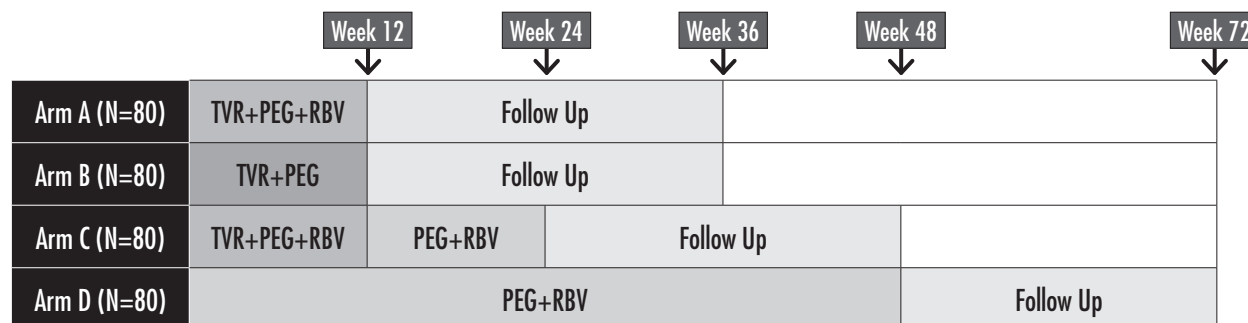
\*Measured by Roche Taqman assay; lower limit of detection is 10 IU/mL

Source:

Jacobson IM, Everson GT, Gordon SG, et al. (abstract 177) Interim analysis results from a phase II study of telaprevir with peginterferon alfa-2a and ribavirin in treatment-naïve subjects with hepatitis C. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 2–6, 2007.

## PROVE 2

**Figure 3. PROVE 2 Study Design (Europe)**



Interim results from PROVE 2 (see Table 4. PROVE 2: Interim Results by Intent-to-Treat Analysis, page 19) emphasize the importance of ribavirin for preventing viral breakthrough. Only 1% to 2% of people who received ribavirin had a breakthrough during treatment (defined as either a > 1-log increase in HCV RNA from the nadir, or an HCV RNA of > 100 after becoming undetectable), whereas viral breakthrough occurred in 24% of the no-ribavirin arm.

**Table 4. PROVE 2: Interim Results by Intent-To-Treat Analysis**

Regimen and N	Undetectable* at week 4	Undetectable* at week 12	Discontinued Tx by week 12	Interim results
Arm A (N=82) TVR + PEG-IFN + RBV for 12 weeks	80%	79%	13% (11/82)	SVR: 59%
Arm B (N=78) TVR + PEG-IFN (no RBV) for 12 weeks	51%	62%	10% (8/78)	SVR: 29%
Arm C (N=81) TVR + PEG-IFN + RBV for 12 weeks, followed by PEG-IFN + RBV for 12 weeks	69%	73%	15% (12/81)	SVR 12: 65% (undetectable 12 weeks after Tx completion)
Arm D - Control (N=82) PEG-IFN + RBV + TVR placebo for 48 weeks	13%	41%	5% (4/82)	Ongoing

\*Measured by Roche Taqman assay; lower limit of detection is 10 IU/mL

Source:

Hezode C, Ferenci P, Dusheiko G, et al. (abstract 80) Prove-2: Phase II study of VX-950 (telaprevir) in combination with peginterferon with or without ribavirin in subjects with chronic hepatitis C, first interim analysis. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 2–6, 2007.

There was a greater incidence of rash, both overall and grade 3, in the telaprevir arms. Although the rash resolved when the drug was stopped, it was severe enough that 3% of the no-ribavirin arm and 7% of the people in the 12- and 24-week arms discontinued treatment. There was a greater incidence of decreased hemoglobin and anemia in the telaprevir arms, especially when combined with ribavirin (Grade 1, 35%; Grade 2, 18%, Grade 3/4, 3%). Gastrointestinal side effects occurred more frequently in the telaprevir arms (Hezode 2007).

Although these results are impressive, given the abbreviated treatment duration, it is important to note that a majority (65–74%) of study volunteers had minimal liver fibrosis (METAVIR of <F2), which may have contributed to the high response rates. Other favorable characteristics may have boosted response rates, such as a low median body mass index (BMI), ranging from 68 to 73 across treatment arms, a high proportion (~40%) of female participants, and an almost exclusively White population (93–99%).

## PROVE 3

Figure 4. PROVE 3 Study Design

	Week 12	Week 24	Week 36	Week 48	Week 72
Arm A (N=110)	TVR+PEG+RBV	PEG+RBV	Follow Up		
Arm B (N=110)	TVR+PEG		Follow Up		
Arm C (N=110)	TVR+PEG+RBV		PEG+RBV	Follow Up	
Arm D (N=110)	PEG+RBV			Follow Up	

Re-treatment options for people who did not respond to pegylated interferon and ribavirin are currently limited to torturous strategies, such as extending treatment with the current standard of care, and doubling doses (see Table 2. Re-treatment Trials in Non-Responders to PEG-IFN and Ribavirin: Strategies and SVR, page 11).

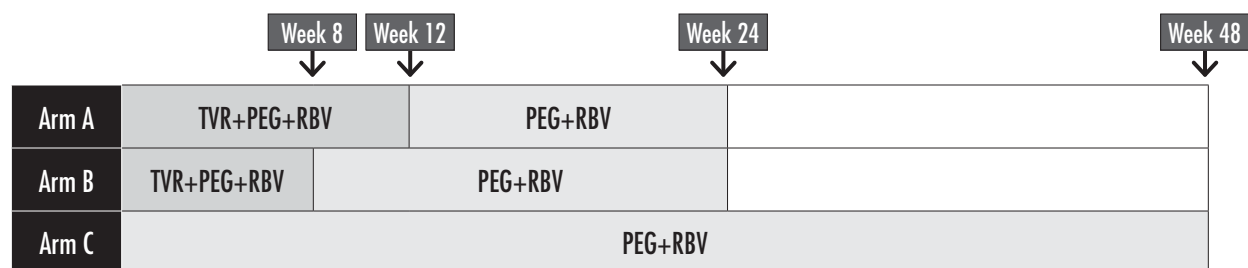
Unfortunately, PROVE 3 will add a single new drug to a previously unsuccessful regimen. At best, this strategy will yield a higher rate of SVR in people who did not respond to re-treatment with pegylated interferon-based regimens. Hopefully, study participants will not be left with drug resistance that limits their future treatment options. If SVR from a telaprevir-based re-treatment regimen surpasses 16% (the highest response to re-treatment of non-responders to pegylated interferon and ribavirin; see Table 2. Re-treatment Trials in Non-Responders to at Least 12 Weeks of PEG-IFN and Ribavirin: Strategies and SVR, page 11), Vertex may seek an indication for use in this population. Unless the results are truly impressive, treatment-experienced people should consider waiting—if possible—until telaprevir can be paired with at least one additional new drug to increase the chance of SVR.

Interim data from PROVE 3 are expected in May 2008; final data will follow a year later.

Meanwhile, Tibotec, Vertex's European development partner, is also conducting a portfolio of phase II studies of telaprevir in people with genotypes 2, 3, and 4, and different dosing schedules of telaprevir (every 8 hours, versus every 12 hours) in treatment-naïve people with HCV genotype 1.

In January of 2008, Vertex announced the phase III development plan for telaprevir. In the first quarter of 2008, they will begin enrolling 1,050 treatment-naïve people who have HCV genotype 1 in ADVANCE, an international, three-arm trial (see Figure 5. Telaprevir Phase III Trial Design, page 21). An additional study will be looking at SVR after 48 weeks of treatment in approximately 400 to 500 people. Final data are expected in 2010, and the company is hoping for FDA approval, for an indication in treatment-naïve people, by 2011.

Figure 5. Telaprevir Phase III Trial Design



- **TMC 435350**

Tibotec and Medivir are co-developing TMC 435350, which has entered phase II. In Europe, TMC 435350 is being studied in both treatment-naïve and treatment-experienced people with hepatitis C genotype 1. This trial is evaluating a seven-day lead-in with different doses of TMC 435350 or placebo, with or without pegylated interferon and ribavirin. The lead-in is followed by 21 days of triple-therapy with TMC 453350 plus pegylated interferon and ribavirin. Participants will subsequently receive 24 or 48 weeks of standard-of-care treatment, according to early treatment response (see Terms for Response to Treatment, page 34).

- **VX-500**

Vertex is developing a second-generation HCV protease inhibitor, VX-500, currently being studied in healthy volunteers. A phase Ib trial in people with HCV is slated to begin in mid-2008.

## HCV Polymerase Inhibitors

There are two distinct classes of hepatitis C polymerase inhibitors—nucleosides and non-nucleosides. Each inhibits HCV replication by a different mechanism; nucleosides are chain terminators, while non-nucleosides cause conformational change. Polymerase inhibitors may have activity across HCV genotypes; they hold great promise, but their Achilles heel is toxicity, which has led to the discontinuation of more than one candidate.

### HCV Polymerase Inhibitors (oral)

Product	Manufacturer	Status
GS 9190	Gilead	Phase I
GSK625433	GlaxoSmithKline	Phase I
PF-00868554	Pfizer	Phase I
R1626	Roche	Phase IIb
R7128	Pharmasset/Roche	Phase I
VCH-759	Virochem	Phase II completed

- **GS 9190**

Gilead has conducted a phase I study of their non-nucleoside polymerase inhibitor, GS 9190, in people with HCV genotype 1. They reported that HCV RNA decreased by more than one log after a single dose, and by almost 2 logs after 8 days of the 120 mg dose (Bavisotto 2007); however, a safety issue emerged: QT prolongation (an abnormality in the heart's rhythm), which may cause fainting, and—in rare cases—sudden death from cardiac arrhythmia. After expert consultation and a separate dose-ranging study in healthy volunteers, the company said that QT prolongation at a lower dose of the drug was "...clinically manageable." Gilead plans to resume development of GS 9190.

- **GSK625433**

An ongoing phase I study is evaluating safety, pharmacokinetics, activity, and tolerability of GSK625433 in healthy volunteers and people with hepatitis C.

- **PF-00868554**

Pfizer is conducting a phase I study of safety, tolerability, pharmacokinetics, and pharmacodynamics of different doses (100, 300, or 450 mg/BID [twice daily] and 300 mg/TID [three times daily] of PF-00868554) in people with HCV genotype 1.

- **R1626**

Roche's HCV nucleoside polymerase inhibitor, R1626, is currently being studied in people with HCV genotype 1. No resistance was detected in study volunteers who received the drug for two weeks by itself, or after four weeks of combination treatment with pegylated interferon and ribavirin (Le Pogam 2007). Although the drug is effective (see Table 5. Week 4 Results from a Phase IIa Study of R1626 plus Pegylated Interferon, With or Without Ribavirin, vs. Standard of Care, page 23), a serious safety issue emerged: grade 4 (severe or life-threatening) neutropenia, which occurred more often in the R1626 arms (Pokros 2007 b). Roche is conducting a phase IIb study with R1626 (500, 1,000, or 1,500 mg/day), and 90 or 180µg of pegylated interferon plus weight-based ribavirin, hoping to identify a safe and effective regimen.

**Table 5. Results from a Phase IIa Study of R1626 Plus Pegylated Interferon, With or Without Ribavirin, Versus Standard of Care**

Study Arm and N	RVR HCV RNA undetectable at week 4	Incidence of grade 4 neutropenia
Dual Low (N=21) R1626 1500mg/day + 180µg PEG-IFN	33%	48%
Dual High (N=32) R1626 3000mg/day + 180µg PEG-IFN	69%	78%
Triple Low (N=31) R1626 1500mg/day + 180µg PEG-IFN & RBV	81%	39%
Standard of Care (N=20) 180µg PEG-IFN & RBV	5%	10%

Source:

Pokros P, Nelson D, Godofsky E, et al. (abstract 67) Robust synergistic antiviral effect of R1626 in combination with peginterferon alfa-2a (40KD), with or without ribavirin—interim analysis Results of Phase 2a study. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 2–6, 2007.

- **R7128**

R7128 is a nucleoside polymerase inhibitor being co-developed by Roche and Pharmasset. They have initiated a phase I trial in healthy volunteers, moving on to dosing in treatment-experienced people with HCV genotype 1. After 14 days of monotherapy with 1,500 mg of R7128, there were reductions in HCV RNA ranging from 1.2 log to 4.2 log (mean of 2.7 log). So far, no serious adverse events have been reported. The most commonly reported side effects were headache and dry mouth (McHutchison 2007). Hopefully, there will be no emergent toxicities as development of R7128 moves forward.

- **VCH-759**

Safety, tolerability, pharmacokinetics, and activity of VCH-759 were evaluated in 32 treatment-naïve people with HCV genotype 1. HCV RNA decreased by more than 1 log regardless of dose, and by more than 2 logs in people who received 800 mg twice or three times per day. There were no serious adverse events or discontinuations during this ten-day study; the most commonly reported side effects were gastrointestinal in nature (Cooper 2007). VCH-759 is currently in phase IIa.

## Other Antiviral Agents in Development

HCV drug development has recently focused on drugs that specifically target the hepatitis C virus—referred to as “STAT-C” (Specifically Targeted Antiviral Therapy for HCV). In addition to the protease and polymerase inhibitors, there are candidates in development that inhibit additional targets: NS5a, alpha-glucosidase, and cyclophilin B.

### Other Antiviral Agents (oral)

Product	Manufacturer	Status
A-831	Arrow Therapeutics/Astra Zeneca	Phase I/II
Celgosivir (MX-3253)	Migenix	Phase II
DEBIO-025	Debiopharm S.A.	Phase II, also studied in HIV/HCV coinfecting people

- **A-831: Hepatitis C NS5a Inhibitor**

Arrow’s A-831, an internal ribosomal entry site (IRES) inhibitor, interferes with the initiation of HCV’s translation process. A phase I study of A-831 has been initiated in healthy volunteers, and a phase I/II study assessing safety, tolerability, pharmacokinetics, and activity in men with hepatitis C is underway; results are expected in 2008. In 2007, AstraZeneca acquired Arrow Therapeutics, Ltd. Since then, there has been no further news about the development of A-831.

- **Celgosivir (MX-3253): Hepatitis C Alpha-Glucosidase Inhibitor**

Alpha-glucosidase inhibitors prevent removal of the glucose residue necessary for the assembly of HCV virions. Migenix’s celgosivir (MBI-3253) is an oral drug made from the Australian black bean chestnut tree. A 12-week viral kinetics study has evaluated the activity of celgosivir and pegylated interferon, with or without ribavirin, versus standard of care, in a group of 57 treatment-experienced persons (null responders (N=11), non-responders (N=36), partial responders (N=21), and relapsers (N=2)) with HCV genotype 1 (see Terms for Response to Treatment, page 34). Early virological response rates were highest in the triple-combination arm (42% versus 10% for standard of care). No additional toxicities or side effects were reported in the celgosivir arms, with the exception of increased flatulence and mild diarrhea (Kaita 2007). An ongoing phase II trial is assessing safety, efficacy, and pharmacokinetics of two doses of celgosivir (400 mg/day and 600 mg/day), plus pegylated interferon and ribavirin, versus standard of care for 12 weeks in treatment-naïve persons with HCV genotype 1.

- **DEBIO-25: Cyclophilin B Inhibitor**

Cyclophilins bind to cellular proteins that regulate the immune system. Cyclophilin inhibitors, such as cyclosporine, are used to prevent post-transplantation organ rejection, but not all

cyclophilin inhibitors have immunosuppressive activity. So far, one candidate, DEBIO-025, is in clinical trials for HCV.

DEBIO-025 is active against hepatitis C and HIV. Safety, pharmacokinetics, and activity of 1,200 mg/day of DEBIO-25 were assessed in a 15-day study of people with HIV, and HIV/HCV coinfection. HCV RNA decreased by at least 2 log in all but one of 19 participants; those with genotype 3 and 4 had larger drops ( $-4.2 \pm 1.1$  and  $-3.4 \pm 1.9$ , respectively) than people with HCV genotype 1 ( $-3.0 \pm 0.9$ ).

Adverse events included abnormally elevated bilirubin (reported in ten participants, four of whom discontinued treatment), and lowered platelet count; all abnormalities resolved upon discontinuation of treatment (Flisiak 2006). An ongoing, five-arm phase II study is assessing safety, pharmacokinetics, and activity of lower doses (400–800 mg/day) of Debio 25 plus standard of care in people with HCV genotype 1 who did not respond to pegylated interferon and ribavirin. Results are expected in mid-to-late 2010.

### **Nitazoxanide: the Upstart**

Avid followers of HCV-specific antiviral agents were surprised by results from a phase II study of nitazoxanide (Alinia®), which was FDA-approved in 2002, to treat diarrhea from two intestinal parasites (*Cryptosporidium parvum* and *Giardia lamblia*).

#### **Nitazoxanide (oral)**

Product	Manufacturer	Status
Nitazoxanide	Romark	Phase II

In part of the sponsor's aptly titled STEALTH-C (Studies to Evaluate Alinia for Treatment of Hepatitis C) program, nitazoxanide was evaluated in a study of 96 treatment-naïve and 24 treatment-experienced people with hepatitis C genotype 4 (see Table 6. STEALTH-C: HCV Genotype 4 Study Design and Interim Results, page 26). An ongoing trial in the US, STEALTH-2, is evaluating a 4-week nitazoxanide lead-in, followed by 48 weeks of pegylated interferon, ribavirin and nitazoxanide versus placebo and standard of care, in 60 treatment-experienced people with HCV genotype 1.

**Table 6. STEALTH-C: HCV Genotype 4 Study Design and Interim Results**

Study Arm and N	RVR HCV RNA Undetectable at Week 4	ETR HCV RNA Undetectable at end of Tx	SVR 12 HCV RNA Undetectable 12 weeks after completion of Tx
Triple: N=40 (Tx naïve=29; Tx experienced=11) 12-week lead-in of nitazoxanide 500mg/twice daily, followed by 36 weeks of nitazoxanide + 180µg PEG-IFN + RBV	Tx naïve = 72% Tx experienced = 27%	Tx naïve = 93% Tx experienced = 36%	Tx naïve = 79% Tx experienced = 25%
Dual: N=40 (Tx naïve=29; Tx experienced=11) 12-week lead-in of nitazoxanide, 500mg/twice daily, followed by 36 weeks of nitazoxanide + 180µg PEG-IFN	Tx naïve = 62% Tx experienced = 27%	Tx naïve = 69% Tx experienced = 45%	Tx naïve = 68% Tx experienced = 8%
Standard of Care: N=40 (Tx naïve only) 180µg PEG-IFN + RBV for 48 weeks	Tx naïve = 35%	Tx naïve = 50%	Tx naïve = 45%

Sources:

Korba BE, Monerto AB, Glenn JS, et al. (abstract 21) Nnitazoxanide: a potent antiviral agent against HBV and HCV. *Frontiers in Drug Development in Viral Hepatitis (HEP-DART)*. Lahaina, Hawaii. December 9–13, 2007.

Romark Laboratories, press release. Available on-line at: <http://www.romark.com/news/11022007.aspx> (accessed 2 March 2008).

Rossignol J-F, Elfert A, El-Gohary Y, Keefe EB. (abstract 178) Interim data from a randomized controlled trial of nitazoxanide-peginterferon-ribavirin, nitazoxanide-peginterferon, and peginterferon-ribavirin in the treatment of patients with chronic hepatitis C genotype 4. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 2–6, 2007.

Without more information on study population (liver histology, baseline viral load, body mass index), adverse events, side effects, and SVR, it is difficult to fully and accurately evaluate these results; hopefully, data from STEALTH-2 will address gaps in data.

## Ribavirin Substitute

- Taribavirin

Taribavirin, the ribavirin prodrug formerly known as viramidine, went back to the drawing board after disappointing efficacy results from phase III studies, VISER 1 and VISER 2.

### Ribavirin Substitute (oral)

Product	Manufacturer	Status
Taribavirin	Valeant	Phase II

An ongoing phase II study is evaluating safety and efficacy of weight-based vramidine (20, 25, and 30 mg/kg/day) vs. weight-based ribavirin, administered in combination with peginterferon alfa-2b to therapy-naïve patients with chronic HCV–genotype 1 infection.

## Anti-Fibrotics

While attention has mainly been focused on viral eradication, some therapies are being developed to slow or prevent additional liver scarring.

### Anti-Fibrotics (oral)

Product	Manufacturer	Status
Farglitazar	GlaxoSmithKline	Phase II
GS 9450 (LB84451)	Gilead	Phase IIa
MitoQ	Antipodean	Phase II
PF-3491390 (IDN-6556)	Pfizer	Phase II

- **Caspase Inhibitors (GS 9450 and PF-03491390)**

GS 9450 and PF-03491390 are caspase inhibitors. Caspase inhibitors block a crucial step in programmed cell death (also called apoptosis), a process that occurs in the liver at higher-than-normal levels in people with chronic hepatitis C and other liver diseases. Inhibiting caspase may lead to decreased fibrosis.

A study of safety, tolerability, efficacy, and pharmacokinetics of GS 9450, Gilead’s once-daily caspase inhibitor, in people with hepatitis C is ongoing in Europe.

In a 14-day study of PF-03491390, liver enzyme levels (ALT: alanine aminotransferase; and AST: aspartate amino transferase) decreased significantly at all doses above 5 mg/twice daily, and normalized in some people who received the drug twice or three times daily. There were no serious adverse events (Pokros 2007a). A larger study is ongoing.

- **MitoQ**

MitoQ was created to protect mitochondria (cellular structures that produce energy). A 28-day phase II study in people with hepatitis C was launched in February 2007 in New Zealand.

- **Farglitazar**

Farglitazar is a peroxisome proliferator-activated receptor (PPAR) gamma agonist. Among their many other functions, PPARs control inflammatory responses in the liver and other parts of the body. An ongoing phase II study is evaluating antifibrotic activity of Farglitazar in persons who could not tolerate, or did not respond to, HCV treatment.

## Immunomodulatory Therapies

- **Toll-Like Receptor Agonists**

Toll-like receptors (TLRs) recognize specific pathogens by patterns on their surface. TLRs signal the immune system by binding to these invaders. Their signal triggers a cascade of responses, activating innate and adaptive immunity. Toll-like receptor agonists stimulate immune responses by binding to TLRs. So far, ten toll-like receptors have been identified. Although two earlier candidates, Actilon and ANA 975, have been discontinued, this approach remains promising.

Stimulating immune responses is a promising approach for HCV therapy, but TLR agonists may be less effective for HIV-positive persons, due to HIV-associated chronic immune activation (Ayash-Rashkovsky 2005).

### **Toll-Like Receptor Agonists (subcutaneous infusion)**

Product	Manufacturer	Status
IMO-2125	Idera Pharmaceuticals	Phase I

- **IMO-2125**

In September 2007, Idera launched a phase I study of IMO-2125 in treatment-experienced people with any HCV genotype.

- **Mono- and Polyclonal Antibodies (Subcutaneous or Intravenous Infusion)**

HCV is universally recurrent after liver transplantation. Hepatitis B immunoglobulin has been successful at preventing recurrent hepatitis B infections in liver transplant recipients, so a similar approach is being used to prevent HCV from recurring after liver transplantation.

### **Mono- and Polyclonal Antibodies (Subcutaneous or Intravenous Infusion)**

Product	Manufacturer	Status
Bavituximab	Peregrine Pharmaceuticals	Phase I, also being studied in HIV/HCV coinfecting people
Civacir	Nabi Biopharmaceuticals/Kedrion	Phase II

- **Bavituximab**

Peregrine Pharmaceuticals is conducting phase I studies of a monoclonal antibody, bavituximab (formerly known as tarvicin), in treatment-naïve and treatment-experienced people with HCV. An additional phase I study is assessing safety, tolerability, pharmacokinetics, and activity of bavituximab in 24 HIV/HCV-coinfecting people. The company is planning to study bavituximab in combination with other anti-HCV therapies.

- Civacir

An ongoing, phase II study is evaluating safety, pharmacokinetics, and efficacy of Civacir (hepatitis C immune globulin) in preventing or lessening the severity of recurrent HCV, in 30 liver transplant recipients. Results are expected in mid-2010.

## Novel Interferon Formulations

Companies have been working on ways to optimize interferon, since it will remain the backbone of HCV treatment for some years. These new formulations of interferon are long-lasting; they may be more effective, and perhaps less toxic than pegylated interferon.

### Novel Interferon Formulations (Subcutaneous Injection or Mini-Pump Device)

Product	Manufacturer	Status
Albuferon	Human Genome Sciences/Novartis	Phase III
Locteron	Biolex Therapeutics/OctoPlus N.V.	Phase IIa
Omega Interferon	Intarcia	Phase II
Peg-Interferon Lambda	Zymogenetics	Phase I

- Albuferon

Albuferon is a formulation of interferon alfa-2b that has been fused to human albumin, to confer long-term exposure from a single infusion. Currently, albuferon is given every two weeks (versus once weekly administration of pegylated interferon, and daily injections of consensus interferon).

Phase II studies have compared different doses and schedules in both treatment-naïve and treatment-experienced people (see Table 7. Albuferon vs. Standard of Care in Treatment-Naïve People with HCV Genotype 1; and Table 8. Albuferon in Non-Responders to Pegylated Interferon Plus Ribavirin, below).

A pair of phase III studies, ACHIEVE 1 (treatment-naïve patients with HCV genotype 1, and ACHIEVE 2/3 (treatment-naïve patients with HCV genotype 2 or 3) are currently underway. However, the 1,200  $\mu\text{g}$  dose has been reduced to 900  $\mu\text{g}$ , due to the greater incidence of serious pulmonary adverse events in the 1,200  $\mu\text{g}$  arm. Efficacy of the 900  $\mu\text{g}$  dose is expected to be equivalent to standard of care, based on data from the treatment-naïve phase II study.

**Table 7. Albuferon vs. Standard of Care In Treatment-Naïve People With HCV Genotype 1 (N=458)**

Regimen	SVR	Discontinued for Adverse Events
Low-dose, every 2 weeks, Albuferon 900µg + RBV	58.5%	9.3%
High-dose, every 2 weeks, Albuferon 1200µg + RBV	55.5%	18.2%
High-dose, every 4 weeks, Albuferon 1200µg + RBV	50.9%	12.1%
Control, PEG-INF + RBV	57.9%	6.1%

Source:

Zeuzem S, Yoshida EM, Benhamou Y, et al. (abstract 180) Sustained virologic response rates with albinterferon alfa-2b plus ribavirin treatment in IFN-naïve, chronic hepatitis C genotype 1 patients. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 2–6, 2007.

**Table 8. Albuferon in Non-Responders to Pegylated Interferon Plus Ribavirin**

Regimen	SVR
Low-dose, every 2 weeks, Albuferon 900µg + RBV	30%
High-dose, every 2 weeks, Albuferon 1200µg + RBV	13%
High-dose, every 4 weeks, Albuferon 1200µg + RBV	25%
Higher-dose, every 2 weeks, Albuferon 1500µg + RBV	9%
Highest-dose, every 2 weeks, Albuferon 1800µg + RBV	17%

Source:

Nelson D, Rustgi V, Balan V, et al. (abstract 51) Sustained virologic response with albinterferon alfa-2b plus ribavirin treatment in prior interferon therapy nonresponders. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 4, 2007.

- **Locteron-interferon**

Locteron-interferon is a continuously released formulation of interferon alfa-2b, currently in phase IIa. SELECT-1 is assessing safety, tolerability, activity, and pharmacokinetics of Locteron, given every two weeks, plus daily ribavirin, in 32 treatment-naïve people with HCV genotype 1. Early results have been presented (see Table 9. Week 12 Results from SELECT-1, page 31). A single, unspecified serious adverse event occurred; otherwise, adverse events were mild, although weakness, joint and muscle pain, and headache were common. More data will be presented at the end of 2008.

**Table 9. Week 12 Results from SELECT-1**

Regimen	EVR (defined as $\geq 2$ log drop)
160 mcg Locteron interferon-alfa 2b + RBV	n/a
320 mcg Locteron interferon-alfa 2b + RBV	88%
480 mcg Locteron interferon-alfa 2b + RBV	100%
640 mcg Locteron interferon-alfa 2b + RBV	n/a

Source:

Dzyublyk I, Yegorova T, Moroz L, et al. (abstract LB10) Phase 2a study to evaluate the safety and tolerability and antiviral activity of 4 doses of a novel, controlled-release interferon-alfa 2b (Locteron) given every 2 weeks for 12 weeks in treatment-naïve patients with chronic hepatitis C (genotype 1). 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. November 4, 2007.

- **Omega Interferon**

The lackluster 37% SVR rate from a phase II study of Omega interferon and ribavirin in treatment-naïve people with HCV genotype 1 has not dissuaded the sponsor, Intarcia, from initiating another trial. They have launched a phase II study, in treatment-experienced people with HCV genotype 1, assessing safety and efficacy of Omega interferon and ribavirin with a novel twist: Omega interferon is administered via the DUROS<sup>®</sup>, an implantable mini-pump.

- **Interferon Lambda**

Interleukin 29, also referred to as interferon lambda, is a synthetic version of an antiviral protein produced by the body. It is being studied with or without ribavirin, in people with hepatitis C who relapsed after treatment with pegylated interferon. Data on safety and activity of different doses, given either once weekly or biweekly, are expected in 2009.

## **Preventive and Therapeutic Vaccines**

- **Preventive**

The phase I study of Chiron's HCV E1/E2 preventive vaccine candidate has been completed; no additional information is available.

### **Preventive Vaccine**

Product	Manufacturer	Status
HCV E1/E2 Vaccine	Chiron	Phase I

- **Therapeutic**

Two therapeutic vaccines were discontinued: Innogenetics halted development of INN-0101, for lack of efficacy; and Novartis stopped HCV E1 E2 due to local and systemic adverse events (joint and muscle pain, weakness, and fatigue). Several other candidates, however, remain in the pipeline.

### Therapeutic Vaccines

Product	Manufacturer	Status
ChronVac-C	Karolinska Institute/Tripep/Inovio	Phase I/II
GI-5005	Globe Immune	Phase II
IC41	Intercell/Novartis	Phase II
PEV2A PEV2B	Previon Biotech	Phase I
TG4040	Transgene	Phase I/II

- **ChronVac-C**

Safety and tolerability of ChronVac-C, a DNA-based therapeutic vaccine, are being studied in treatment-naïve people with HCV genotype 1 and a low hepatitis C viral load. ChronVac-C is administered with a brief electrical pulse (a process called electroporation) that creates temporary pores in cell membranes that allow the vaccine to enter cells. Data are expected in 2009.

- **GI-5005**

GI-5005 is a yeast-based vector expressing hepatitis C NS3 and core proteins, and is intended to stimulate the immune system to clear HCV-infected cells. A phase I study reported immune responses in 23% of participants, as measured by ELI-Spot. ALT normalization occurred in 50% of the highest-dose cohort, and 11% of participants had decreases in HCV RNA, ranging from 0.7 to 1.4 log (Schiff 2007). A phase II study of GI-5005 is being conducted in 120 people with HCV genotype 1, who are either treatment-naïve or non-responders to previous therapy, comparing 48 weeks of GI-5005 plus pegylated interferon and ribavirin to 48 weeks pegylated interferon and ribavirin.

- **IC41**

IC41 uses synthetic T-cell peptides with a polyarginine adjuvant to prime the immune response. Phase II results were encouraging; IC41 significantly reduced hepatitis C viral load in treatment-naïve people with HCV genotype 1. Intercell and Novartis are planning further studies of IC41.

- **PEV2A PEV2B**

PEV2A PEV2B uses man-made antigens to stimulate helper (CD4 cell) and killer (CD8 cell) immune responses. An ongoing phase I study is assessing safety and immune responses in healthy volunteers.

- **TG4040**

TG4040 uses a modified viral vector (MVA: modified vaccinia Ankara) to target immune responses to HCV's NS3, NS4, and NS5B proteins. It is being studied in treatment-naïve and treatment-experienced relapsers. Results of these phase I studies are expected by the end of 2008.

## Terms for Response to HCV Treatment

**Treatment Response:** Response to hepatitis C treatment is measured by change in HCV viral load at different time points. Since it is a common practice to release interim data from HCV treatment trials, it is important to understand what these terms mean, so that interim results can be properly interpreted. It is important to consider the threshold of detection of the test used to measure HCV viral load, since these thresholds vary widely. The most sensitive tests can detect >5 copies IU/mL.

**RVR (Rapid Virological Response):** RVR means that there is no detectable hepatitis C virus in the blood after 4 weeks of treatment. An RVR is a good indication of SVR, but it is not as accurate for predicting who is unlikely to have SVR. Therefore, HCV treatment should not be discontinued if there is no RVR. RVR is mainly used in research.

**EVR (Early Virological Response):** EVR means that hepatitis C viral load has dropped by 99% (2 logs), or is undetectable after 12 weeks of HCV treatment. An EVR is a good predictor of the ultimate response to HCV treatment. If a person does not have an EVR, their chance of SVR is very low (1-4%). Usually, HCV treatment is discontinued in people who do not have an EVR.

**ETR (End-of-Treatment Response):** ETR means that there is no detectable hepatitis C virus in the blood at completion of HCV treatment. The ETR is usually higher than the SVR rate, because the hepatitis C virus may reappear in a person's blood after completion of HCV treatment.

**SVR (Sustained Virological Response):** SVR means that there is no hepatitis C virus detectable in the blood six months after a person completes HCV treatment. Many experts regard SVR as a cure, and it is an indication of long-term remission. SVR rates are always lower than response rates from earlier time points.

**SVR-12:** SVR-12 means that there is no hepatitis C virus detectable in the blood 12 weeks after completion of HCV treatment. Although it has not been prospectively validated, many experts agree that relapse (meaning the emergence of detectable hepatitis C virus in blood after completion of treatment) is most likely to occur within 12 weeks. However, FDA and other regulatory agencies require 24 weeks of post-treatment follow-up before a person is considered to have achieved an SVR.

**HCV Treatment History:** There is a growing population of people who did not have a sustained virological response from HCV treatment. They are sometimes referred to as "treatment failures," but the term "treatment-experienced" is preferable, although both are not sufficiently specific.

It is important to know how treatment-experienced people responded to their first course of treatment, and the regimen that they were treated with, because these factors help to predict the likelihood of SVR from re-treatment. People initially treated with standard interferon, or standard interferon plus ribavirin, may achieve SVR when re-treated with pegylated interferon

and ribavirin. Sometimes, HCV re-treatment trials study a mixed population of relapsers, partial responders, non-responders, and null responders, which makes it difficult to interpret the results.

**Null Responder:** A null responder is someone who achieves little or no decrease in hepatitis C viral load during HCV treatment. Null responders are highly unlikely to respond to re-treatment with an interferon-based regimen.

**Non-responder:** Often referred to as a “treatment failure,” a non-responder is someone who does not have an EVR or, if they stay on treatment for 24 weeks, does not ever have a 2-log (99%) drop in hepatitis C viral load or undetectable HCV RNA during hepatitis C treatment.

**Partial Responder:** A partial responder is someone who experiences at least a 2-log decrease in hepatitis C viral load during HCV treatment. Partial responders are more likely to respond to re-treatment than non-responders or null responders.

**Relapser:** The term relapser refers to someone who has had an EVR or ETR, but whose virus rebounded after they completed HCV treatment. People who had a relapse after completing HCV treatment are more likely to achieve SVR after re-treatment than partial responders, non-responders, or null responders.

## RESOURCES

### About clinical trials:

[www.clinicaltrials.gov](http://www.clinicaltrials.gov) (accessed on March 4, 2008).

### About HCV drug development and research:

HCV Advocate ([www.hcvadvocate.org](http://www.hcvadvocate.org)) offers conference reporting and an up-to-date HCV pipeline chart, available on-line at: <http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs.html> (accessed on March 4, 2008).

HIV and Hepatitis.com offers news and conference reports: [www.hivandhepatitis.com](http://www.hivandhepatitis.com) (accessed on March 4, 2008).

NATAP (National AIDS Treatment Advocacy Project) offers comprehensive information on HCV research and drug development: [www.natap.org](http://www.natap.org) (accessed on March 4, 2008).

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# TAG

Treatment Action Group

A-831 • Albuferon • Bavituximab •  
ChronVac-C • Civacir • DEBIO-025  
GS 9450 (LB84451) • GSK625433 • H  
ITMN-191 (R7227) • Locteron Interferon  
(Celgosivir) • Nitazoxanide • Omeg  
PEV2A PEV2B • PF-00868554 • PF-34  
Taribavirin • Telaprevir (VX-950) • TG40