



## Report from DDW 2005 – Part 1



Alan Franciscus, Editor-in-Chief

*The Digestive Disease Weekly (DDW) conference was recently held in Chicago, IL. This conference followed the recent European Association for the Study of Liver Disease (EASL) and much of the information released at EASL and subsequently reported in the May 2005 issue of the HCV Advocate was also covered at DDW. For this reason, we will only be covering any new or updated information presented at the recent DDW conference. There was a variety of noteworthy information on many areas of hepatitis C. Part one of this report will focus on new drug therapies, HCV medical treatment for patients with HCV-related decompensated cirrhosis, diabetes and the HCV knowledge and practices of internal medicine residents.*

### INVESTIGATIONAL THERAPIES

In last month's HCV Advocate I reported on the data from three new therapies to treat hepatitis C – viremagine, valopicitabine (NM 283) and albuferon. Viremagine (in combination with pegylated interferon) is a prodrug of ribavirin. The data on the effectiveness of viremagine was similar to the group that was treated with ribavirin (in combination with pegylated interferon). Valopicitabine is an oral nucleoside analog – a new class of drugs that directly inhibit the

hepatitis C RNA polymerase. The preliminary results from the 24 week data found that there was a 99.0% decrease in HCV RNA (viral load). Albuferon is a form of time released interferon that was found to produce a 99.9% decrease in HCV RNA (viral load) with 23% of the same patients remaining HCV RNA negative. The information from EASL on these new therapies and possibly improved therapies to treat hepatitis C seemed very promising. Building on the positive news from EASL, there was even more information on new HCV drugs presented at DDW. The highlight of the conference was information about VX-950, a new HCV protease inhibitor.

### VX-950

VX-950 is an oral protease inhibitor of the hepatitis C virus discovered by Vertex Pharmaceuticals. The mechanism of action of VX-950 is to inhibit an enzyme of the hepatitis C virus responsible for viral replication. If the hepatitis C virus can not make additional copies it can possibly be eradicated.

In this study, a total of 8 healthy volunteers and 34 HCV patients were treated with VX-950 in three different dosing arms – 450 mg every 8 hours, 1250 mg every 12 hours or 750 mg

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every 8 hours or placebo for 5 and 14 days. All patients in the HCV positive group genotype 1 (the most difficult to treat) were either previous non-responders to HCV treatment or patients who had never been treated. It was reported that VX-950 was well-tolerated with no serious side effects that required discontinuation of therapy. It was also noted that there were no elevations of ALT or AST liver enzymes in the treated patients. Across all of the treatment arms patients achieved at least a 1,000-fold reduction of hepatitis C RNA (viral load). The dosing arm that was most effective was the 750 mg arm which achieved a median viral load reduction of 25,000 fold in 4 out of 8 patients. Two patients achieved viral load reductions below the level of detection.

Vertex reported that based on these positive results they are planning further studies using VX-950 monotherapy as well using it in combination with currently approved medications to treat hepatitis C.

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# Adherence to HCV Therapy



Alan Franciscus, Editor-in-Chief

Adherence to HCV therapy is one of the most important predictors of a successful treatment outcome. While there are well defined and established adherence guidelines for other disease states such as HIV, hypertension and other diseases, it is less clear when it comes to adherence for HCV Therapy. There is an established threshold of 80% for HIV, which means that if a patient does not take 80% of the medications, 80% of the time, the chance of a successful treatment outcome is greatly diminished. There have been retrospective (analyzing data from previous trials) studies on hepatitis C treatment adherence that have been able to establish the 80/80/80 rule. This means that people taking hepatitis C medications are less likely to have a successful treatment outcome if they do not take 80% of interferon, 80% of ribavirin, for 80% of the time. However, the 80/80/80 rule is controversial because it has not been studied in well-designed prospective clinical trials. Another concern is that the 80/80/80 rule may be sending the wrong message about treatment adherence since it sets a lower threshold for taking medications rather than encouraging people to take 100% of the medications, 100% of the time or as close to 100% as possible.

Currently, pegylated interferon and ribavirin do not cause HCV resistance so the question of adherence is only important right now in terms of treatment outcomes. However, the questions of adherence will become even more important in the future with the development of antiviral therapies such as HCV protease and helicase inhibitors, where, as seen with HIV, viral mutation and resistance are known problems.

We do know that it is important to take as much of the prescribed medications as possible, but this can be difficult considering the moderate to severe physical and psychological side effects of HCV therapy. There are a number of predictors of adherence to HCV therapy that are well recognized as important and this article will discuss strategies to help people achieve successful treatment adherence. It is also important to remember that not everyone will have a successful treatment outcome even with 100% adherence to HCV therapy.

## **BELIEF IN TREATMENT**

One of the most important predictors of successful treatment outcome is belief in the medications being used to treat hepatitis C. If people believe that they will have a successful treatment outcome they will be more likely to take the important steps needed for successful treatment.

## **BUILDING A RELATIONSHIP WITH MEDICAL PROVIDERS**

Another important strategy is to build a strong and open minded relationship with your medical provider; that is, one which is nonjudgmental and non-threatening, provides appropriate education, encourages the use of support systems, regularly evaluates psychosocial status, and takes a proactive approach to the management of treatment side effects. It is important that people develop a relationship with the entire medical team – not just the doctor. In these times of managed health care, medical support staff may be actually managing your care more closely than your physician.

## **CUSTOMIZE TREATMENT REGIME**

It is important to customize the treatment regimen to meet the patient's lifestyle so as to make treatment part of, not all of, their lives. When feasible, people should be encouraged to continue working while they are on therapy as work can help distract from the side effects and may increase their chances of staying on therapy. One specific strategy is to time the injections of pegylated interferon to coincide with potential side effects. For example, for a person who works Monday through Friday, injecting the pegylated interferon on a Friday night provides the weekend to rest up in case there are more side effects one or two days after the injection. Another strategy is to include pill organizers that can help keep track of when to take the ribavirin and any other medications.

## **MEDICAL PROVIDERS' EXPERIENCE**

Another key component of adherence is managing the side effects of treatment before they become so severe that dose reduction or discontinuance of HCV medicines would be necessary. There are several factors that will increase the likelihood of successfully managing treatment side effects, including the experience of the treating medical provider in managing side effects as well as the patient self-reporting the side effects in a timely manner. The HCV Advocate Web site has many side effect management fact sheets that provide a wealth of information about common strategies to help with side effect management. However, it is very important that the side effects are always managed by a medical provider. The final decision on

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# HealthWise:

## *HCV Treatment and Reproduction Issues*



Lucinda K. Porter, RN, CCRC

*There are two main reproduction issues associated with current treatment for hepatitis C virus infection (HCV). One is pregnancy, the other is breastfeeding. It is important to understand these issues before you begin treatment as these will affect you before, during, and after treatment.*

### REPRODUCTION

When ribavirin was combined with interferon and tested on animals, it was linked to birth defects and fetal death. Because of this, the Food and Drug Administration (FDA) has strict requirements for companies selling ribavirin. Ribavirin is a category X drug. This means it may cause birth defects or death to a fetus. There are bold warnings printed on the labels for the two most frequently prescribed brands, Copegus™ and Rebetol®.

If you are female, your doctor or nurse should verify that you are not pregnant immediately before you start treatment. This means taking a pregnancy test. If you are male, you will be asked to confirm that your female partner is not pregnant. If you have the starter kit that accompanies Copegus™, a urine pregnancy test is supplied to enable you to do this. If you don't have a starter kit or you have the kit that comes with Rebetol®, you will have to obtain a test through your doctor or drugstore.

Assuming pregnancy is ruled out, then the goal is to avoid pregnancy throughout treatment and for six months after treatment has been stopped. The guidelines are to use two reliable forms of birth control. Birth control should be used in situations where pregnancy is even remotely possible. This includes women who have had tubal sterilizations and men have had vasectomies. Technically the only conditions in which pregnancy is impossible are for women who are post-menopausal or who have had a hysterectomy. According to the Menopause Guidebook published by the North American Menopause Society, menopause is defined as the permanent end of fertility marked by the absence of any menstrual bleeding for 1 year (assuming there are no other causes).

Notice the use of the word reliable when discussing birth control. Reliable means using medically accepted

contraceptive methods and using them correctly. Whatever you choose, make sure you are well-informed on how to use the method correctly. Also notice the word **two**. *This means that if you use two forms of birth control and one fails, then you have back-up protection.*

If pregnancy occurs during or six months after treatment has stopped, report this immediately. Tell your medical provider. All pregnancies should be reported to the Ribavirin Pregnancy Registry. You or your doctor can do this. This is confidential, free, and important. (*See Resource Section*)

### Types of Birth Control (The higher percentage is with perfect use)

- Abstinence – 100% reliable, but since it's impractical, include a back-up method
- Tubal Sterilization – 99.5-99.9% reliable
- Vasectomy – 99.5-99.9% reliable
- Condom – 85-98% reliable, nearly 100% with withdrawal
- Female condom – 79-95% reliable
- Spermicide – 71-85% reliable
- Diaphragm – 84-94% reliable
- The "Pill" – 92-98% reliable
- The "Patch" – 92- > 99% reliable
- The "Ring" – 92- > 99% reliable
- The "Shot" – 97-99.7% reliable
- IUDs – 99- > 99% reliable
- Fertility Awareness – 75-99% reliable, include a back-up method for fertile days
- Withdrawal – 73-96% reliable

Below are examples of two reliable forms of contraception, where vasectomy is considered one method and tubal ligation another.

- A man with a vasectomy whose post-procedure infertility has been confirmed plus a correctly used condom

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**Actilon**

Actilon (CPG 10101) is a member of a new class of drugs that induces the body's natural types of interferon to help restore immune function. The data on two randomized, placebo-controlled dose escalation (5 different doses injected subcutaneously) studies of 42 HCV positive people who were non-responders to a previous course of HCV therapy were reported. The greatest decline in viral load was seen in the group receiving the 20 mg dose. Five of the six patients receiving the 20 mg dose twice weekly achieved a 96% reduction in HCV viral load in 4 weeks. While on the therapy five of the six patients in this arm achieved at least a 90% reduction in HCV viral

load. The drug was generally well-tolerated. The side effects reported were injection site reactions and mild flu-like symptoms. The authors concluded "early antiviral activity has been demonstrated with CPG 10101" and "safety results suggest that higher doses for a longer treatment period are tolerable." Further studies examining CPG 10101 both as monotherapy and in combination with interferon plus ribavirin therapy are being planned.

**PEG-alfacon**

Data from a phase 1 clinical trial of PEG-alfacon (pegylated IFN alfacon 1 – a time released form of consensus interferon) was presented at DDW which showed that PEG-alfacon was safe and well-tolerated in healthy individuals and that further studies are warranted in patients with hepatitis C.

**InterMune's HCV Protease Inhibitors**

Information from pre-clinical studies was presented on InterMune's two HCV protease inhibitors currently under development. It was found that in vitro (in a test tube) these two drugs were stable and targeted the liver in the preclinical models. Additional testing of these compounds is being planned.

The results of all of these studies are very encouraging. The dramatic reduction in HCV RNA (viral load) in the VX-950 study and the NM 283 study reported last month show great promise for future HCV treatments. However, all of these drugs are in early clinical development and the effectiveness and tolerability of these new drugs will not be known until larger clinical trials are enrolled, conducted and completed – which could

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# New Targets for Anti-HCV Therapy



Liz Highleyman

*In order to understand the potential for new drugs to treat hepatitis C, it is useful to look at the lifecycle of the hepatitis C virus (HCV). HCV is a small virus consisting of a single-strand RNA (ribonucleic acid) genome encased in a capsid shell and surrounded by an envelope, or membrane.*

## THE HCV LIFECYCLE

HCV can only reproduce after it enters a host cell and takes over the cell's machinery. The steps in HCV replication are attachment to the host cell, entry into the cell, uncoating, translation of the RNA genome into viral proteins, protein cleavage and processing, HCV genome replication, and assembly and release of new virus particles (virions). Agents that interfere with any step in this process can potentially be developed as therapies for hepatitis C.

## ENTRY INHIBITORS

HCV's lipid (fat) envelope consists of two glycoproteins, E1 and E2. The viral envelope attaches to a host cell's outer membrane and the virus is then incorporated into the cell. It is unclear which receptors HCV uses to bind to host cells, but the low-density lipoprotein (LDL) receptor and the CD81 cell surface receptor are thought to play a role. Researchers are working on several agents that interfere with virus-cell attachment by blocking either cell receptors or viral envelope proteins (e.g., the monoclonal antibodies HepeX-C and HuMax-HepC), but such drugs are not likely to be available soon. Agents that prevent uncoating are also potential drug candidates.

Once HCV enters a cell, it sheds its envelope and its capsid degrades, releasing its genetic material into the cell's cytoplasm (intracellular material). Unlike some other viruses such as HBV and HIV, HCV does not integrate its genetic material into the host cell's genome, so there's a better chance that HCV can be eradicated.

## PROTEIN TRANSLATION

HCV then takes over the host cell's replicative machinery – the ribosomes – to synthesize its own proteins. The virus binds to ribosomes by means of an internal ribosomal entry site (IRES) located at one end of its genome. An important early step in this process is the assembly of a replication complex (or replicase), where gene translation (protein production) takes place. HCV messenger RNA acts as a blueprint for the translation of 10 viral proteins. Some pharmaceutical companies are working on agents that target the IRES and messenger RNA. These include antisense oligonucleotides (short sequences of genetic material that bind to RNA and block its use), ribozymes (enzymes that cut RNA), and small interfering RNA sequences (siRNA) that bind to viral RNA and target it for destruction. Examples include ISIS-14803 (an antisense oligonucleotide) and Heptazyme (a synthetic ribozyme). These agents are at early stages of development and are not likely to be available for at least a few years.

## PROTEASE INHIBITORS

The gene translation process produces long polyprotein chains that must be cut up, or cleaved, into smaller pieces before they can be assem-

bled into new virions. Enzymes called proteases act as “molecular scissors” to perform this task. In addition to two host cell proteases, HCV also uses two viral proteases called NS2-3 and NS3-4A. The second protease cleaves RNA at multiple sites and is an attractive target for drug development. The success of HIV protease inhibitors suggests that this is a promising approach. Experimental anti-HCV agents in this class include BILN-2061, VX-950, Schering Plough's SCH-6 and SCH-7, and two early compounds being developed by InterMune.

Some of the newly cleaved protein pieces must be processed before they can be used to assemble new virions. For example, the E1 and E2 envelope proteins must have sugars added (glycosylation) and must be attached to form structures called heterodimers. Agents that interfere with these processes – such as castanospermine and Celgosivir (MBI-3253) – can also play a role in inhibiting HCV replication.

## GENOME REPLICATION

In order to form a new virus particle, HCV must replicate its genome. To do this, the original positive-strand, or “sense,” RNA sequence is used as a template to produce a mirror-image negative-strand, or “antisense,” sequence. This, in turn, acts as a template to construct new complementary positive-strand RNA segments, which will be the genomes for new daughter virions.

Two viral enzymes facilitate this process. The NS5B RNA-dependent RNA polymerase (NS5B RdRP) is responsible for assembling new chains

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take as long as 5 to 15 years depending on the current stage of clinical development.

The bottom line is that people should not delay or stop therapy based on these results because the odds of any new drug moving from clinical development to FDA marketing approval for treating any disease is very low.

### TREATMENT – PATIENTS WITH DECOMPENSATED CIRRHOSIS

Treating people who are in end-stage disease (decompensated cirrhosis) can be difficult because current HCV medications can accelerate the decompensation or the disease progression process. However, people with decompensated cirrhosis are the ones who are in the most need for treatment to help delay or stop further deterioration of the liver. Previous studies have found that people with decompensated liver disease can be successfully treated in research settings under careful observation. In addition, it has been found that even in this difficult to treat population that some people will achieve a sustained virological response (SVR-HCV undetectable during and six months post treatment) and improvement in liver health.

A study by Kim et al was presented at DDW on a trial of 32 patients with decompensated cirrhosis. Treatment consisted of pegylated interferon plus ribavirin (78.1% of patients), pegylated mono-therapy (12.5% of patients) or interferon plus ribavirin (9.4%) for an average of 37.8 weeks.

In addition, all of the patients were treated for complications of cirrhosis (ascites and varices) prior to starting HCV therapy to optimize liver function. All of the patients were closely monitored within a major university transplant program for possible complications. Growth factors to manage treatment related side effects were used.

The overall SVR rate reported was 31.3% (genotype 1 – 21.1% SVR; 53.8% SVR in non-genotype 1 patients). As the result of treatment, 5 patients (15.6%) in this study were removed from the transplant listing due to improvements in liver func-

*“Most alarming was that 20.3% reported that they vaccinated HCV negative individuals with an HCV vaccine.”*

tioning. No patient died as the result of therapy.

A total of 84.4% of patients in this study experienced some form of adverse event with six patients (18.8%) requiring discontinuation of therapy and one patient was required to discontinue therapy due to liver decompensation. The most common side effects included anemia, neutropenia, depression and infections.

The authors concluded that “antiviral therapy appears to be safe and effective in carefully selected patients with decompensated cirrhosis” and that “treatment may result in SVR in nearly one-third of patients.” This is very encouraging news for patients with end-stage disease who currently have very few options other than liver transplantation.

### DIABETES AND HCV

It is well known that people infected with hepatitis C are at a higher risk for developing Diabetes Mellitus than the general population even though the direct link between the hepatitis C virus and diabetes has not been proven. However, many experts believe that there is either a direct viral mechanism involved or that the hepatitis C virus indirectly causes or increases the likelihood of developing diabetes.

V. Khurana et al reported on a large retrospective study of about a half a million U.S. veterans to investigate the statistical association between HCV and diabetes. Information was collected from October 1998 to June 2004 on 480,306 veterans – 91.7% were males. The average age in this study was 61.1 years. Of these, 103,256 (21.5%) had diabetes and 14,021 (2.92%) had hepatitis C.

After analyzing the data the authors found that in people who are infected with hepatitis C there is a 48% increased risk of diabetes even after controlling for other well known diabetes risk factors – age and body mass index.

### PHYSICIAN KNOWLEDGE AND HCV

Previous studies have found that among first year residents the knowledge of hepatitis C is very low, with many first year interns misinformed about hepatitis C. What is worrisome about the lack of knowledge is that this group of physicians is the next generation who will identify, evaluate and manage people with hepatitis C.

In a study conducted by J.K. Lim et al, a 1-page survey assessing the knowledge and practices concerning hepatitis C infection was given to 251 internal medicine residents at 8 ACGME-accredited U.S. Training programs. The residents were equally

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distributed among three post-graduate years. 89.6% were U.S. medical graduates enrolled in traditional (64.9%) or primary care (22.7%) programs and 98% had seen patients with hepatitis C within the past year (60.6% had seen more than 10 patients within this timeframe).

**The key findings were:**

- *Screening for HCV*
  - ◆ Most screened for hepatitis C in patients with abnormal ALT's (85.3%), prior needlestick exposure (82.1%), prior injection drug use (80.9%) or HIV infection (77.7%), but many did not screen for other at risk populations, including people with a history of blood transfusion (59.8%), snorting cocaine (26.7%) or incarceration (21.5%)
- *Performed a viral load test*
  - ◆ 45.5% performed HCV PCR (viral load) test
- *Performed a genotype test*
  - ◆ 36.7% performed a genotype test
- *Vaccinated HCV positive individuals against HAV and HBV*
  - ◆ 33.1% vaccinated against HAV
  - ◆ 61.4% vaccinated against HBV
  - ◆ 19.5% were familiar with HAV vaccine schedule and 64.5% for HBV vaccine schedule
  - ◆ Most alarming was that 20.3% reported that they vaccinated HCV negative individuals with an HCV vaccine.
- *HCV and liver transplantation*
  - ◆ 30.7% named HCV as the #1 reason for liver transplantation
- *Knowledge about factors that influence HCV disease progression*
  - ◆ Alcohol (80.5%)
  - ◆ HIV (75.3%)
  - ◆ HBV (64.1%)
- *Knowledge about genotype information*
  - ◆ 25.5% identified genotype 1 as the most common in the U.S.
  - ◆ 22.3% identified genotype 1 as the least responsive to therapy
- *Knowledge about medicines to treat HCV*
  - ◆ 35.5% identified interferon/ribavirin or pegylated interferon/ribavirin therapy as the 1<sup>st</sup> line of antiviral therapy
  - ◆ 30.7% incorrectly named lamivudine (used to treat HBV) as a therapy for HCV

- *Knowledge about HCV disease progression*
  - ◆ 10.0% correctly estimated the rate of chronic infection after exposure
  - ◆ 14.7% correctly estimated the risk of developing cirrhosis at 20 years of infection
- *Self-knowledge about HCV*
  - ◆ 23.9% reported that they feel adequately trained in HCV management.

The authors concluded that “many internal medicine residents receive inadequate training in the management of chronic HCV infection. Most lack basic knowledge regarding epidemiology, natural history, diagnosis, clinical course and treatment of HCV. Targeted educational interventions are needed to address knowledge deficits among future primary care physicians.”

Hopefully as more and more physicians become educated about hepatitis C, the lack of knowledge or misinformation among some physicians will be reversed. Until then, it is extremely important that all patients educate themselves as much as possible about HCV disease management so that they can receive the best possible medical care when they partner with their medical providers.

**DONOR REGISTRY**

Every day in the U.S. 17 people die waiting for a transplant. As of March 30, 2005, there were 87,847 people waiting for organs in this country. This number grows daily. To address this, California now has an online donor registry. This is in addition to the pink dot that is currently on your driver's license. Just registering is not enough. You need to talk to your family and communicate your wishes to them. Organs are chosen based on their condition, so anyone of any age and with any disease may be a potential donor. Minors between the ages of 13 and 17 are allowed to register, but their parents are legally responsible for the ultimate decision. One of the lessons that the Terry Schiavo case taught many of us is to put important decisions in writing. Please don't wait until faced with the unthinkable to make this decision. A single donor can save up to 8 lives, and improve the quality of almost 50 more!

To register, go to [www.donateLIFECalifornia.org](http://www.donateLIFECalifornia.org)  
Give the gift of life... be an organ donor!"

## HEALTHWISE

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- A woman who underwent tubal sterilization whose partner uses a condom correctly
  - A man who correctly uses a condom with a spermicidal
  - A woman who correctly uses a diaphragm with a spermicidal
  - A man with a vasectomy and a woman with a tubal ligation

*For information about emergency contraception, talk to your medical provider or contact Planned Parenthood.*

### Important Points

- Rule out pregnancy prior to starting HCV treatment
  - Use **two** reliable forms of birth control during and six months after treatment
    - Whatever method you choose, know how to use it correctly
    - Report any pregnancy immediately

## BREASTFEEDING

Nursing mothers who want to undergo HCV treatment must choose either breastfeeding or treatment. They should not do both at the same time.

### Resources

Ribavirin: Pregnancy Registry 1-800-593-2214; 1-910-509-4991 (Call collect) [www.ribavirinpregnancyregistry.com](http://www.ribavirinpregnancyregistry.com)  
 Planned Parenthood: 1-800-230-PLAN or 1-800-230-7526 [www.plannedparenthood.org/pp2/portal/medicalinfo](http://www.plannedparenthood.org/pp2/portal/medicalinfo)  
 Hoffman-La Roche (Pegasys™ and Copegus™): 1-877-PEGASYS (1-877-734-2797) [www.pegasys.com](http://www.pegasys.com)  
 Schering Plough (PegIntron® and Rebetol®): 1-888-HEP-2608 (437-2608) [www.pegintron.com](http://www.pegintron.com)



## ADHERENCE

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how to treat side effects should always be made by the medical team.

### KEEPING APPOINTMENTS

It is very important that the person being treated keeps medical appointments and that blood work is routinely performed so the medical provider can monitor any potential problems.

### SOCIAL SUPPORT

Staying on treatment sometimes involves pulling together all the resources that are available. This includes as much support as possible from family, friends and employers. It is highly recommended that a support system be put in place well before the start of therapy. One critical aspect necessary to successful treatment adherence and outcome is attending a support group. Support groups can provide the invaluable emotional support that is so needed while on therapy. There will be some members of the support group who have been on therapy and they can help with strategies for maintaining your health and managing side effects while on treatment.

### THE MOST VALUABLE TOOL

People with hepatitis C have the most valuable tool available – themselves – to help make treatment outcomes successful by being proactive in the management and treatment of HCV by using all the resources available to them including family, peers, nurses, physicians’ assistants, nurse practitioners, case managers, pharmacists, psychologists and patient support programs.

The strategies discussed above can help give people a better chance for a successful treatment outcome. However, there are many other factors that influence treatment outcome, such as the type of treatment, HCV genotype, weight, HCV viral load, as well as age

## ANNOUNCING WEB BASED CME ACCREDITATION COURSE

The HCV Advocate Online Education Center CME Courses are intended for physicians specializing in gastroenterology, internal medicine, and hepatology, as well as other healthcare professionals conducting research and/or providing care for individuals with diseases of the liver.

### Overview

This CME course, Diagnosing HCV, is an interactive web course that provides comprehensive information on the diagnosis of HCV infection. Participants can test their knowledge of the material through study questions at the end of each section. By combining up-to-date clinical and epidemiological information this web-based training program provides a valuable educational tool to assist health professionals in the complex task of diagnosing HCV infection.

### Course: Diagnosing HCV

Visit <http://www.hepeducate.org> for more information.

and race. It is important to remember that not everyone can achieve treatment success no matter how adherent they are to treatment. Although we should all strive for 100% adherence to HCV treatment medications, no one is perfect and there will be times when a person will forget to take a pill or may miss an injection by one day. There is nothing to be gained by playing the “blame game” if they are they are not 100% adherent – we are only human and perfection is an ideal not a reality. Remember to give it all you have, but don’t forget to be gentle with yourself.



## TARGETS

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of nucleotides (adenine, cytosine, guanine, and uracil, the basic building blocks of RNA). Several experimental agents inhibit the action of NS5B RdRP. Some, called nucleoside or nucleotide analogs, act as defective building blocks; when they are added to a growing RNA chain, they prevent the addition of more nucleotides and production comes to a halt (thus, they are also known as “chain terminators”). Valopicitabine (NM-283) and isatoribine (ANA245) are examples of experimental nucleoside analogs. Ribavirin and its successors (e.g., viremagine, levovirin) are also nucleoside analogs, but they also have other types of antiviral activity as well. In addition, there are experimental non-nucleoside polymerase inhibitors – such as Japan Tobacco’s JTK-003 and JTK-109 – that act by other mechanisms.

Once produced, the new RNA sequences tend to bind to one another; when this happens, they can no longer be used for further replication. The NS3 helicase enzyme (in conjunction with the NTPase enzyme) acts as a “wedge” to keep RNA segments from pairing up. Helicase inhibitors interfere with this process and thus block viral replication. Several companies are exploring HCV helicase inhibitors, but there are no approved drugs in this class for any disease.

## ASSEMBLY AND BUDDING

After the new RNA genomes are produced, they must be assembled into daughter virions. These new viral particles then “bud” out from the host cell – taking parts of the cell’s membrane with them as an envelope – and go on to infect other cells. Agents that interfere with assembly or budding (e.g., UT-231B) thus also have potential as anti-HCV therapies.

## HOPE FOR THE FUTURE

Research on HCV-specific antiviral agents has been hampered by the fact that the virus does not go through its complete replication cycle in laboratory cell cultures; in addition, there are no good small animal models that can be used to screen anti-HCV drug candidates. However, there has been recent progress in this area with the development of HCV “replicons” that can be used to study some of the steps of the replication process. As researchers learn more about how HCV enters host cells and reproduces, new agents that target specific viral activities will no doubt be discovered.

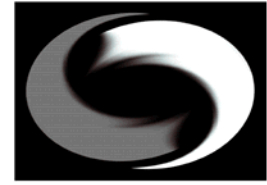
Drugs that specifically target HCV are less likely to cause systemic (whole body) side effects such as those seen with interferon. But because the HCV replication process is prone to error, the virus can mutate to develop resistance against agents that target specific steps in its life cycle. Fortunately, using a combination of different drugs that target different phases of HCV replication can force the virus to mutate extensively, potentially making it weaker and less infectious. For this reason, combination therapy will likely prove more effective and more durable than single agents.

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SUPPORT PROJECT**

### Executive Director Editor-in-Chief, HCSP Publications

Alan Franciscus  
[alanfranciscus@hcvadvocate.org](mailto:alanfranciscus@hcvadvocate.org)

### Managing Editor, Webmaster

C.D. Mazoff, PhD  
[cdmazoff@hcvadvocate.org](mailto:cdmazoff@hcvadvocate.org)

### Contributing Authors

Liz Highleyman  
Lucinda K. Porter, RN, CCRC

### Design and Production

Paula Fener  
Blue Kangaroo Design  
[blueroodesign@aol.com](mailto:blueroodesign@aol.com)

### Contact information:

Hepatitis C Support Project  
PO Box 427037  
San Francisco, CA 94142-7037

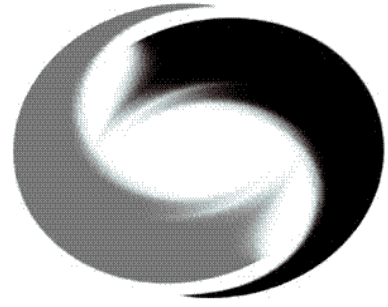
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P.O. Box 427037  
San Francisco, CA  
94142-7037