

# Update on New Therapies



Alan Franciscus, Editor-in-Chief

March was a disappointing month for results from two new drugs in clinical development to treat hepatitis C – Albuferon, and Viramidine. Problems from side effects of another new therapy, valopicitabine (NM 283) have prompted the company to revise the clinical trial to allow a lower dose of the medication. However, all three drugs are still considered strong potential treatment candidates – but they will all require more studies at different doses to establish safety and effectiveness.

## ALBUFERON

Albuferon is a form of time-released interferon that is produced by fusing human serum albumin to interferon. Preliminary results found that Albuferon was safe and well-tolerated and had the potential to treat hepatitis C in doses administered (by injection) every four weeks instead of the once a week injection of pegylated interferon. Unfortunately, preliminary results from a phase IIb study comparing Albuferon plus ribavirin vs. pegylated interferon (Pegasys) plus ribavirin found that one dose every 4 weeks of Albuferon plus daily ribavirin produced lower treatment response rates than the once weekly dosing of pegylated inter-

feron (Pegasys) plus daily ribavirin. However, there was a slightly higher treatment response in the group that injected Albuferon every 2 weeks. Another disappointing result was the higher drop-out rates in the high dose Albuferon group – 7.6% vs. 2.6% in the Pegasys group. However, the company is still optimistic and will move forward with larger trials. The full interim results will be presented at the upcoming European Association for the Study of Liver Disease (EASL) 2006 Conference.

If two week dosing is effective it begs the question – will one once every two weeks instead of once weekly be enough to compete with the two well-established drugs (Pegasys and Peg-Intron)?

## VIRAMIDINE

Results from the Phase 3 VISER 1 trial of Viramidine (prodrug of ribavirin) versus ribavirin (both in combination with Peg-Intron) in treatment naïve patients (never received treatment) found that the safety profile (hemolytic anemia) of Viramidine was superior to ribavirin. The other study endpoint of effectiveness of Viramidine vs. ribavirin didn't fair as well.

In this study 970 patients (worldwide) were treated with



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Peg-Intron plus a fixed dose of Viramidine (600 mg) vs. a Peg-Intron plus weight based dose of ribavirin (1000/1200 mg). Treatment duration was 48 weeks for participants with non-genotype 2 and 3 and 24 weeks for genotype 2 and 3 patients. Post treatment follow-up was 24 weeks.

## RESULTS

**Anemia:** It was found that the anemia rates (hemoglobin less than 10 g/dL) were statistically lower in patients treated with Viramidine than in patients treated with ribavirin (5% vs. 24%,  $p < 0.0001$ ).

**Sustained Virological Response:** In the intent to treat (ITT) analysis of 637 patients treated with Peg-Intron plus Viramidine vs. Peg-Intron plus ribavirin the SVR was 38% vs. 52% for the ribavirin group. When the data was broken down per protocol the SVR rates were 51% (Viramidine) vs. 56% (ribavirin)

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# HCV Treatment Eligibility for Injection Drug Users



Alan Franciscus, Editor-in-Chief

Injection drug users comprise the largest patient population with hepatitis C. Prior to 2001 the National Institutes of Health (NIH) Consensus Statement on the management of Hepatitis C excluded anyone from HCV treatment who had used illegal drugs or alcohol 6 months prior to starting HCV therapy. In 2002, the NIH removed these exclusion criteria and recommended that medical providers “determine on an individual basis whether patients who use drugs or alcohol may be offered treatment.” However, most medical providers still use the older criteria of abstinence 6 months prior to starting HCV therapy to exclude most drug users. Up until now there has been little research to establish how many drug users would be eligible for HCV therapy if the restrictive criteria were used to deny HCV treatment.

In a current article titled “Eligibility for Treatment of Hepatitis C Virus Infection among Young Injection Drug Users in 3 US Cities,” published in the journal *Clinical Infectious Diseases* in March 2006, Holly Hagan and colleagues studied a group of drug users in three cities (Baltimore, MD, New York, NY and Seattle, WA) to find out how many drug users would be eligible for HCV treatment based on the restrictive criteria most widely practiced by the medical community.

The enrollment period of the study of young IDUs was from June 2002 to February 2004 in Balti-

more, New York and Seattle. In order to be eligible for the study the participants had to test positive for the HCV antibody, to have injected drugs in the past 6 months, be negative to HIV and be between 18 -35 years old. Participants were assessed for depression, using the Beck Depression Inventory (a score > 19 indicates moderate to severe depression), alcohol consumption, using the Alcohol Use Disorders Identification Test (AUDIT – a score of > 8 indicates a drinking problem), HCV RNA (viral load), and abnormal ALT levels. It was noted that, since currently used parameters for ALT levels are not a sensitive measurement of liver injury, the upper limit of ALT was adjusted to reflect an upper healthy limit. The upper limit of healthy was revised to 0.75 times the normal upper limit for men and 0.63 times the upper limit of normal for women. For example if the lab report listed the upper limit of normal ALT as 40 IU/mL for men, the adjusted upper healthy limit would be 30 IU/mL (.75 times 40 IU/mL = 30 IU/mL); the upper healthy limit for women would be 25.2 IU/mL (.63 times 40 IU/mL = 25.2 IU/mL).

## RESULTS

A total of 632 eligible patients were enrolled. Sixty-four percent of the study participants (404) were HCV RNA (viral load) positive. Heroin, alone or with cocaine, was the drug mainly injected by the study

participants. The patient characteristics were male (78%), White (60%), median age was 26 years old (interquartile range 23-29), number of years injecting was 6 years (interquartile range 4-9), those who had never been incarcerated (84%), and those who had never been in drug treatment of some type (70%). Only 23% reported they were currently enrolled in a drug treatment program. Sixty-five percent of the injectors in this study reported that they injected drugs daily. Twenty two of the 404 participants (55%) scored < 19 on the Beck Depression Inventory, and 255 of the 404 (63%) scored < 8 on the Alcohol Use Disorders Identification Test. Forty-four out of 404 (11%) had not injected drugs in the previous 30 days. A total of 335 injectors had ALT levels above the healthy limit and 279 of 404 (69%) had ALT levels above the normal limit.

Based on the criteria for ALT level, Beck Depression Inventory score, and AUDIT score **only 4%** of the injectors in this study were considered eligible for HCV treatment.

Commenting on the restrictive criteria, the authors noted that there is no credible scientific basis to deny treatment to injection drug users. The reasons for denying treatment are largely based on misinformation such as:

- Re-infection of HCV if a person returns to injection drug use.

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# HealthWise:

## *Healthy Living with HCV Series*

### *Part 1: The Food Pyramid*



Lucinda K. Porter, RN

Have you ever heard the expression, “We are what we eat”? Yesterday I was fruit, vegetables, whole grains and fish. I made healthy choices because I nearly committed gastrointestinal suicide the previous day with too much chocolate and Dim Sum. Although my mouth still wanted more chocolate, my body felt much better after I ate healthier food.

“What should we eat?” is commonly asked by people living with chronic hepatitis C virus infection (HCV). There are various opinions about this, some sensible and some not. One of the most heated discussions our HCV support group ever had was on the subject of diet. I think it was the only time that people in the group raised their voices.

I do not believe that diets are one size fits all. We each need to find a nutritional plan that we can follow. Religion, ethics, geography, seasons, taste preferences, money, allergies, and health all influence what we eat. The best diet is the one that fits you.

The United States Departments of Agriculture (USDA) along with Health and Human Services (HHS), released new nutritional guidelines in 2005. These guidelines included a new food pyramid. Although most experts agree that the new pyramid is an improvement over the old ones, controversy surrounds the pyramid. Critics believe that special-interest groups influenced the pyramid design and details. These include the National Dairy Council, Soft Drink Association, American Meat Institute and National Cattlemen’s Beef Association.

One problem with the 2005 food pyramid is that it is still vague. It does not stress the importance of choosing plant-based foods. At first glance, it does not emphasize avoiding trans fats. Although it advises limiting sodium intake, it does not explain that processed foods tend to be high in sodium. Some say that the dairy recommendations are too high, possibly showing the influence of the dairy council rather than solid

research.

The USDA’s food pyramid is not the only available guide. Frustrated by the USDA’s inadequate guidelines, the Harvard’s School of Public Health created the *Healthy Eating Pyramid*. (See *Resources* for more information) The Harvard pyramid differs from the USDA’s in that it builds a foundation on daily physical activity and weight control. Oldways, a food think tank organization, offers pyramids for Asian, Mediterranean, and Latin diets. These alternatives emphasize unrefined and plant-based foods.

Here are highlights of the USDA guidelines:

- *Emphasizes fruits, vegetables, whole grains, and fat-free or low-fat milk and equivalent milk products. Specifically, many fruits and vegetables are packed with nutrients but have very few calories.*
- *Includes lean meats, poultry, fish, beans (legumes), eggs, and nuts.*
- *Is low in saturated and trans fats, cholesterol, salt (sodium), and added sugars.*
- *Balances calorie intake with calorie needs.*<sup>1</sup>

The USDA’s website personalizes the food pyramid ([www.mypyramid.gov](http://www.mypyramid.gov)). It is easy to use, but you have to have access to the Internet. Most local libraries offer free Internet service. Here is an example of a personalized plan using a 50-year-old moderately active female. Daily recommendations are based on a 2000-calorie diet:

- 3 cups of low-fat or fat-free milk or yogurt
- 2 cups of fruit
- 2.5 cups of vegetables
- 6 ounces of grains – at least half of them whole
- 5.5 ounces of protein – choose a variety from

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**STATE OF WASHINGTON ORGAN DONATION:**

Although there is a shortage of donated livers, there are also other organ shortages. Upon death, one has the potential to donate the heart, kidneys, lungs, pancreas, spleen, intestine, skin, bone, veins, lymph nodes, the entire eye or just the cornea, and soft tissue, such as ligaments, tendons, and muscle. Instead of the entire liver, sometimes only liver cells are used for transplantation purposes.

At this time, the state of Washington does not maintain its own organ registry. Washington residents are encouraged to tell their loved ones about their preferences. It is recommended that they indicate their wishes on their driver's license or state identification. Washington residents may also register online at the Living Legacy Registry web site at *www.livinglegacyregistry.org*

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# Psychological and Social Aspects of Hepatitis C Treatment



Liz Highleyman

Most studies of hepatitis C reported in the medical literature concern various aspects of natural history, disease progression, and treatment. But psychological and social factors can also have a profound effect on people with hepatitis C. A few recent journal articles have explored these issues.

## PROBLEMS ARE COMMON DURING TREATMENT

A majority of patients with hepatitis C experience some type of difficulty – physical, mental, or social – when using interferon-based therapy. As reported in the April 2006 *European Journal of Gastroenterology and Hepatology*, a team led by Susan Zickmund, MD, a researcher at the University of Pittsburgh and the Veterans Affairs Medical Center, interviewed 65 HCV patients. As is typical for the population of hepatitis C patients seeking treatment, the average age was 46 and about 62% were men. In this group, 80% described moderate to severe problems associated with treatment. Most were physical problems – 74% reported fatigue and 32% had flu-like symptoms – but more than one-third (38%) experienced depression.

In addition, about one-third said they had to quit their jobs or cut back on employment due to side effects. One-fifth said side effects contributed to deteriorat-

ing relationships with friends and family, and 22% said lifestyle adjustments related to treatment (such as not drinking alcohol or the need to rest more often) caused “friction” with friends. “To encourage appropriate levels of adherence,” the researchers concluded, “healthcare providers should seek information about these indirect treatment effects as they monitor their patients on therapy.”

In the March 2006 *Journal of Hepatology*, Amy Dan of Inova Fairfax Hospital in Virginia and colleagues looked at depression, anemia, and health-related quality of life (HRQOL) in 271 people with chronic HCV receiving pegylated interferon (Peg-Intron) plus ribavirin. Similar to Zickmund’s study, the average age was 47 and 69% were men; nearly three-quarters were white. The researchers found, as expected, that anemia and depression both led to decreased HRQOL. Symptoms of depression tended to increase over the first half of the course of treatment. Patients with cirrhosis, obese patients, and women reported more quality-of-life impairment; however, age, race/ethnicity, ALT levels, and HCV viral load levels were not associated with differences in HRQOL. While HRQOL declined during treatment, it typically returned to – or exceeded – the pre-treatment level within 24 weeks after completion of therapy.

## SERIOUS PSYCHIATRIC ILLNESS

While any patient taking interferon can experience reduced quality of life, the risk is higher in certain groups including substance users and people with pre-existing mental illness. Due to the adverse mental side effects – especially depression – associated with interferon, experts have traditionally recommended that patients with serious pre-existing psychiatric illness should not be treated, and these patients have been excluded from most clinical trials of anti-HCV medications. However, just as studies have shown that injection drug users can achieve good adherence and treatment response rates (see “Treating Hepatitis C in Injection Drug Users” in the May 2005 *HCV Advocate*), researchers are also finding that hepatitis C treatment can be successful in people with pre-existing mental conditions.

In the April 2006 issue of *Psychosomatics*, Lisa Mistler, MD, from Dartmouth College and associates presented a comprehensive literature review of hepatitis C treatment in people with severe mental illness and depression. While most studies suggest that mild to moderate depression symptoms occur in 20%-40% of patients treated with interferon, less than 10% develop severe interferon-induced major depres-

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## PSYCHOLOGICAL AND SOCIAL

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sive disorder. Studies to date offer conflicting evidence as to whether interferon-induced depression is more common in people with a history of psychiatric illness. While changes in energy level (fatigue) typically occur within days of starting treatment, changes in mood and cognition “tend to occur weeks or months” after treatment begins.

Several studies have shown that antidepressant medications are effective in preventing or relieving depression during interferon therapy, both for those with and those without a history of pre-existing mental illness. For example, in the June 2005 *Journal of Hepatology*, Martin Schaefer and colleagues reported that patients with pre-existing psychiatric conditions who started a selective serotonin reuptake inhibitor (SSRI) antidepressant (citalopram or Celexa) before HCV treatment were significantly less likely to develop major depression during the first six months of interferon therapy, compared with those who did not receive the antidepressant (14% vs 64%, respectively).

A smaller number of patients (2%-16% in various studies) report new or worsening anxiety during treatment with interferon. Studies suggest that most such patients can complete treatment. Mistler and colleagues concluded that interferon-induced anxiety “appears to be mild and uncommon.” Other psychiatric conditions (including mania or psychosis) are rare among patients taking interferon, and there is little data about whether problems during HCV treatment are more common or more severe among patients

with pre-existing conditions. But it is clear that these conditions usually abate when interferon is discontinued.

People with severe mental illness “can be safely and effectively treated for hepatitis C virus,” the authors concluded, and thus should be offered interferon-based therapy if indicated based on degree of liver disease progression. “[N]europsychiatric side effects are, in some cases, preventable, and, in most cases, treatable,” they continued. “Severe neuropsychiatric side effects due to [interferon] are uncommon and reversible.”

### GOOD MANAGEMENT IS THE KEY

When conventional interferon monotherapy offered only about a 10% chance of a cure for hepatitis C, many patients and healthcare providers felt the reduction in quality of life related to treatment was not worth the risk. But with today’s improved therapies, the risk/benefit balance has shifted. Sustained response rates can reach as high as 70%-80% for patients with HCV genotypes 2 or 3, and 50-60% for those with genotype 1. As such, it’s more important than ever to find ways to help patients start and stick to treatment – and there’s less justification for automatically excluding any groups from therapy (although treatment may not be appropriate for certain individuals within these groups).

In their overview, Mistler and colleagues concluded that hepatitis C patients with severe mental illness could achieve “good treatment adherence, low drop-out rates, and good side-effect tolerability” provided they are offered “assertive psychiatric management, close monitoring, and adjustment of psychiatric medica-

tion to address the psychiatric side effects.” But patients with no history of mental conditions or only mild psychiatric problems should also be monitored for depression, given that some studies suggest interferon-induced depression is just as common among people without such a history.

One of the ironies of hepatitis C is that sometimes you have to feel worse in order to feel better. If depression, fatigue, or other treatment side effects are interfering with your job, relationships, ability to care for children, or other aspects of your daily life, talk to your healthcare provider. In many cases, adjunct therapies (such as antidepressants, or EPO for anemia) may allow you to stay on treatment. Sometimes social support from family and friends is the best medicine. Many HCV positive people find that peer support groups can be a lifeline before, during, and even after treatment. To find a support group in your area, see the HCV Advocate web site’s Community and Support section ([www.hcvadvocate.org/community/community.asp](http://www.hcvadvocate.org/community/community.asp)). For practical tips on dealing with depression and fatigue, see the Hepatitis C Support Project’s booklet *Coping with Depression and Hepatitis C* ([http://www.hcvadvocate.org/hepatitis/About\\_Hepatitis\\_pdf/1.1.1\\_Living\\_With\\_HepatitisC/Depression.pdf](http://www.hcvadvocate.org/hepatitis/About_Hepatitis_pdf/1.1.1_Living_With_HepatitisC/Depression.pdf)) and *A Guide to Understanding and Managing Fatigue* ([www.hcvadvocate.org/hepatitis/factsheets\\_pdf/Fatigue\\_guide.pdf](http://www.hcvadvocate.org/hepatitis/factsheets_pdf/Fatigue_guide.pdf)).



## IDU

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- ◆ Studies have shown that when injection drug users are treated and counseled about prevention that the re-infection rate is very low.
- Lower treatment response because of drug and alcohol use.
  - ◆ We do know that heavy alcohol and drug use during treatment will lower the treatment response rates, but we do not have studies that have shown that low to moderate alcohol and drug use dramatically reduces the chances of successful treatment
- Pre-existing depression that could be exacerbated by interferon treatment
  - ◆ Injection drug users are more likely as a group to have depression before treatment, but studies have consistently shown that as long as depression is well controlled most people can stay on and complete HCV treatment.

As discussed above, the majority of current and prior HCV infections are the result of injection drug use. The benefits of treating active injection drug users include:

- Stopping the spread of HCV
  - ◆ By reducing the pool of HCV infected persons the overall infection rates will be reduced.
- Addressing a public health problem
  - ◆ HCV infection is one of the largest infectious disease problems in the United States and treatment in the 'core' group can reduce the future disease burden of hepatitis C.
- Providing overall medical care to drug users which will decrease future illness and disease burden

◆ Treating injection drug users for HCV could also be a bridge for other health-related problems and a bridge to addiction treatment.

It was also noted, that since active injection drug users are generally younger and have less severe liver damage, the chances of responding to current HCV treatment is higher.


In an accompanying editorial, Brian R. Edlin and Michael R. Carden discuss various barriers related to prevention, management and treatment of active injection drug users. The authors comment that the core group of hepatitis C positive individuals has been largely ignored by the scientific community. Instead most scientists focus on the "convenient populations." The authors concluded that "until these barriers are overcome, the HCV epidemic will continue to spread unabated, and morbidity and mortality from liver disease will continue to rise."

**References:**

"Eligibility for Treatment of Hepatitis C Virus Infection among Young Injection Drug Users in 3 US Cities," by Holly Hagan and colleagues. *Clinical Infectious Diseases* 2006;42:669-72

"Injection Drug Users: The Overlooked Core of the Hepatitis C Epidemic," by Brian R. Edlin and Michael R. Carden. *Clinical Infectious Diseases* 2006;42:673-6





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## New Test for Acetaminophen Toxicity



Alan Franciscus, Editor-in-Chief

In the United States there are more than 56,000 emergency room visits related to acetaminophen (also known as paracetamol and by the brand name Tylenol) toxicity and which accounts for approximately 500 deaths each year, making acetaminophen-related toxicity the leading cause of acute liver failure. Tylenol is considered safe taken at the recommended doses even in people with hepatitis C. However, acetaminophen is also an ingredient in more than 600 separate prescription and non-prescription products so people may not realize that they are taking more than the recommended daily dose.

Now scientists have developed a blood test that measures for "serum acetaminophen-protein adducts" or mutations that are specific biomarkers for acetaminophen drug related toxicity. In an analysis of 66 people who died from liver failure, the biomarkers found that acetaminophen toxicity was responsible for 20 cases. Interestingly, the biomarkers were also seen in 7 of 36 indeterminate cases and the researchers speculated that, based on the biomarkers, these 7 cases could have been caused by acetaminophen.

The bottom line is to make sure you check the product label, and if acetaminophen is listed as an ingredient to factor it in and not take more than the recommended daily dose. For more information see HCSP's Fact Sheet *Acetaminophen and Your Liver*.



## NUTRITION

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beans, nuts, seeds, fish, poultry and lean red meat

- 6 teaspoons of vegetable oil
- Limit extra fats and sugars to 265 calories

Serving sizes have increased over the years. So has the size of Americans. If weight is an issue for you, practice portion control. Three ounces of meat is the size of a deck of playing cards. One serving of cereal is the size of a fist. A slice of bread equals a cassette tape. A pancake serving equals a CD. An ounce and a half of cheese is roughly equivalent to four stacked dice. A teaspoon of margarine equals a single die. A serving of ice cream is the size of a half a baseball. Two tablespoons of peanut butter equals a ping-pong ball. A cup of vegetables is about the size of a baseball. A quarter cup of raisins is roughly the size of a large egg.

Here are guidelines upon which many nutrition experts agree:

- Avoid trans fats. These can be found in margarine, shortening, fast and processed foods. Examine labels for *partially hydrogenated vegetable oil*. This means trans fat. Check cookie and cracker labels for trans fats.

- Strive for a diet that is low in saturated fat. Butter, cheese, ice cream, whole milk, and red meat are typical sources of saturated fat. Avoid or limit foods using palm and coconut oil. Skip fried foods, especially deep-fried.

- Eat lots of fresh fruit and vegetables. Make colorful choices as produce from each color group targets certain vitamins and minerals. Juice and dried fruits are high in calories and are not adequate replacements for fresh fruit.

- Opt for grains that are whole rather than processed. Those who avoid white food tend to eat a high fiber diet.

- Choose plant-based proteins. When eating animal protein choose fish and poultry rather than red meat.

- Minimize intake of foods with added sugar.

- Select a variety of foods.

- Do not exceed sodium levels that are recommended for your health condition.

- Drink 6-8 glasses of water daily.

- Do not eat more calories than you use, unless you need to gain weight.

Two more recommendations specifically for patients with liver disease are:

- Avoid raw or undercooked shellfish.

- Do not eat wild mushrooms unless you are 100% sure of what you consume.

Raw or undercooked oysters or clams can carry *Vibrio vulnificus*, bacteria that cause a number of serious clinical conditions. Uncooked shellfish may also harbor hepatitis A. Certain wild mushrooms contain toxins that can destroy even the healthiest livers.

In addition to maintaining a nutritional diet, strive to practice safe food habits. Food poisoning is a serious problem in our country. Hepatitis A can be a food or water borne virus. It is recommended that those with hepatitis B and C be immunized against hepatitis A. (It is also recommended that those with HCV infection receive the hepatitis B vaccine.) For specific guidelines about food hygiene, try the consumer advice icon at 1-888-

SAFEFOOD (1-888-723-3366) [www.foodsafety.gov](http://www.foodsafety.gov)

*Next month: Physical Fitness*

### Resources

**Center for Science in the Public Interest** – This non-profit education and advocacy group works to protect consumer interests. (202) 332-9110 [www.cspinet.org](http://www.cspinet.org)

**Harvard School of Public Health** – Offers an alternative food pyramid, as well as nutrition and healthy lifestyle information. [www.hsph.harvard.edu/nutritionsource/index.html](http://www.hsph.harvard.edu/nutritionsource/index.html)

**Oldways** – This organization promotes itself as a food issue think tank. Offers alternative pyramids for a variety of diets, including Mediterranean, Latin, Asian, and vegetarian. (617) 421-5500 [www.oldwayspt.org](http://www.oldwayspt.org)

**Physicians Committee for Responsible Medicine** – This organization focuses on preventative medicine, ethical use of animals and humans in research and provides information about vegetarian diets. (202) 686-2210 [www.pcrm.org](http://www.pcrm.org)

**United States Department of Agriculture** – This website offers interactive tools for personalizing nutritional goals. 1-888-7PYRAMID (1-888-779-7264) [www.mypyramid.gov](http://www.mypyramid.gov)

**United States Health and Human Services** – Good place to start looking at government based nutrition recommendations. [www.health.gov/dietaryguidelines](http://www.health.gov/dietaryguidelines)

### Reference

<sup>1</sup><http://www.health.gov/dietary-guidelines/dga2005/healthieryou/html/chapter6.html>



## NEW THERAPIES

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in North America and Europe. In these regions Viramidine met the non-inferiority criteria. The company is questioning the data from other areas which they think may have negatively affected the total trial results. In addition, Valeant believes that if Viramidine was weight dosed (like ribavirin in this trial) that Viramidine would have produced similar SVR rates to ribavirin. The complete data set (genotype, age, ethnicity and viral load) will be presented at the EASL 2006 Conference in late April.

Another phase III study of Viramidine – VISER 2 is comparing Pegasys plus Viramidine to Pegasys plus ribavirin and is currently underway. Preliminary data from this trial is expected towards the middle of 2006. It will be interesting to see if the FDA will approve Viramidine for marketing based on the superior safety profile or if the FDA will require further testing of Viramidine in higher doses or dosed by body weight. Valeant hopes to launch Viramidine by the end of 2007.

## VALOPICITABINE

Valopicitabine is currently in two different phase III studies for treating hepatitis C. Due to gastrointestinal-related adverse events in the treatment naïve trial of the 800 mg dose of valopicitabine plus Pegasys about 16% of patients discontinued treatment and 3 patients developed serious adverse events. This represents 2% of the valopicitabine-treated patients. In the second trial of valopicitabine (used as a monotherapy and in combination with Pegasys) for previously treated patients, 5% of valopicitabine treated patients discontinued treatment due to gastrointestinal

side effects, and six serious adverse events were reported (4% of valopicitabine treated patients). Due to the incidence of gastrointestinal adverse events Indenix and the FDA have amended the original clinical trial design to reduce the dosage of valopicitabine to either 200 or 400 mg depending on the study group. According to a company spokesperson, “While these modifications will delay the valopicitabine development program, the primary purpose of phase II studies is to identify the optimal dosing regimen with respect to efficacy and safety. Meaningful data from these ongoing trials, along with data from the planned ribavirin interaction study and potential additional dose-ranging data, which is expected to be available over the next six months, will provide us with necessary safety and efficacy data to further define the phase III development plan for valopicitabine.”

Bringing a new drug to market is a long and expensive process. The reason for clinical trials is to provide information about a drug’s safety and effectiveness. It is not uncommon to find that doses have to be adjusted as more information about the effectiveness and side effects of the drugs come to light. The data from the three drugs above does not necessarily mean that the new drugs will not be viable treatments for hepatitis C in the future, but we will not know how effective the drugs are until data from phase III trials is completed and submitted to the Food and Drug Administration. Even then we may have to wait for a good period of follow-up time to find out if the SVRs achieved are durable over time.



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

Alan Franciscus  
alanfranciscus@hcvadvocate.org

**Managing Editor, Webmaster**

C.D. Mazoff, PhD  
cdmazoff@hcvadvocate.org

**Contributing Authors**

Liz Highleyman  
Lucinda K. Porter, RN, CCRC

**Design**

Paula Fener  
Blue Kangaroo Design  
blueroodesign@aol.com

**Contact information:**

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

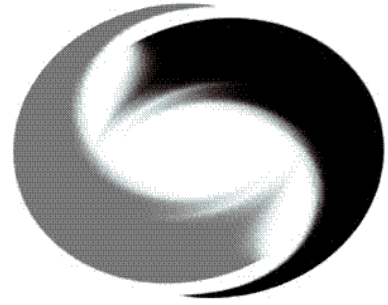
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