

Hepatitis C *Review*

NATAP ❖ 580 Broadway Suite 1010 ❖ New York NY 10012 ❖ 212 -219- 0106 ❖ 1- 888- 26 NATAP ❖ email: info@natap.org ❖ www.natap.org

The Medical Management of Hepatitis C

Heather Wilantewicz, RPA-C
Director of Clinical Services
The PATH Center
The Brooklyn Hospital Center



Hepatitis C virus (HCV) has become a significant cause of morbidity and mortality in people living with HIV. Due to similar transmission risk factors, coinfection with both viruses is common. In the United States, there are about 3 times more people with chronic HCV than HIV. Nationally,

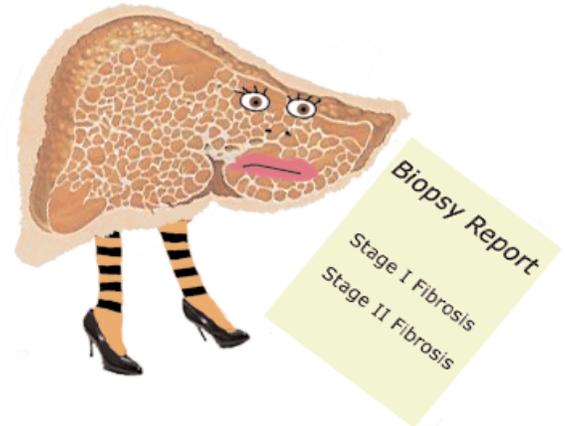
about 1 out of 4 HIV positive people have HCV. All HIV positive patients should be tested for HCV and evaluated for possible treatment.

"Hepatitis" means inflammation of the liver. HCV is a virus spread by contact with HCV infected blood. Over time, the HCV virus can cause scars to form on the liver making it unable to work properly. There is no vaccine to prevent HCV and HCV often has no symptoms. You could be infected with HCV and not know it. The most common symptom is fatigue. Other symptoms may include mild fever, muscle and joint aches, nausea, vomiting, loss of appetite and vague abdominal pain. These symptoms are called non-specific, meaning you would not know they are associated with HCV.

A HCV antibody test is a blood test used to screen for HCV. The antibody test is positive if someone was exposed to HCV virus. Approximately 15% of people will clear the HCV spontaneously without medications. Their antibody test will stay positive forever. Therefore, a Hepatitis C viral load test is needed to confirm infection. If there is HCV virus in the blood, then the person has HCV. If your CD4 count is low, your immune system may not be able to produce a positive antibody test. A HCV viral load test should then be ordered if there are unexplained liver enzyme elevations or risk factors and HCV is suspected. HCV viral loads are often in the millions but do not correlate with the severity of one's liver disease or its progression. When a person receives HCV treatment, the viral load is then used to assess response to HCV treatment.

Each HCV client is individually evaluated for HCV treatment, which consists of combination therapy with weekly injections of pegylated interferon and daily ribavirin pills taken twice a day with food. Liver enzyme and liver function tests are

Maybe it's time to consider treatment like Fanny Fibrosis?



checked if you have HCV but can be normal even if there is liver damage. The HCV genotype is a blood test that tells the type of strain that you have. There are 6 major genotypes, 1 to 6. The genotype helps to predict response to therapy and to determine the length of treatment necessary. Genotype 1 is the most common in the United States and is the hardest genotype to treat. Genotypes 2 and 3 have much higher cure rates. Genotypes 4-6 are less common in the United States. An alpha-feto protein blood test and abdominal sonogram are used to screen for liver cancer. A high alpha-feto protein test means that there is liver injury but doesn't necessarily mean that there is liver cancer. The abdominal sonogram is a painless imaging procedure in which a probe is moved over the outside of the abdomen and sends sound waves that reflect off of the internal organs and produce pictures of the organs on a screen. This test will check for liver masses.

None of the above tests accurately tell the extent of the liver disease or predict the rate of progression. The liver biopsy is the gold standard for knowing the extent of a person's liver disease and ruling out other liver diseases. During the liver biopsy, a needle is inserted into the liver and a small amount of liver tissue is obtained under local anesthesia. The liver sample is looked at under the microscope for inflammation and fibrosis (scarring). The procedure takes less than a couple of seconds. The longest part of the liver biopsy is waiting in the recovery room afterwards where you are monitored for pain and any rare bleeding. In most cases, you are sent home the same day. The liver biopsy may be optional in genotypes 2 and 3 since the rates of clearance are so high that treatment of these genotypes is recommended regardless of the biopsy result.

NATAP NATIONAL AIDS TREATMENT ADVOCACY PROJECT
EDUCATING COMMUNITIES ABOUT HIV AND HEPATITIS

The info contained in this newsletter is provided for educational purposes only and does not constitute medical advice and should not be used as such. NATAP does not practice medicine. We recommend in all cases an individual should consult a physician prior to pursuing any course of treatment.

HCV medication is not for everyone. You will not be able to take HCV medications if you have certain medical conditions. Since HCV therapy can exacerbate any pre-existing medical or psychiatric conditions, a thorough clinical and laboratory evaluation is necessary. A complete blood count, kidney function tests, glucose, thyroid function tests, autoimmune tests, iron studies, chest x-ray, EKG, substance use screening and ophthalmologic examination are done. Pre-treatment psychiatric monitoring is necessary to assess for pre-existing depression and mood disorders, which will need to be addressed before treatment. Depression and mood disorders can occur or worsen while on treatment, and close monitoring of a patient's mental health is critical throughout therapy. Since ribavirin can cause birth defects, it is extremely important that women, and women of male partners taking HCV therapy do not get pregnant while on treatment and for 6 months after the treatment ends. The medication is still in your body for months after stopping treatment.

The major drug interaction between HIV and HCV medications is between ribavirin and didanosine (videx). Ribavirin increases the levels of didanosine (ddl) in the body and can lead to serious toxicities. It is not advised to take the two together. If you are taking videx, your healthcare provider will need to substitute another HIV drug if possible.

The decision of who to treat for HCV can be challenging. All patients, including those who did not cure their virus with non-pegylated interferon therapy, are considered for pegylated interferon and ribavirin therapy. Patients who meet the guidelines for HIV therapy generally are first started on antiretroviral therapy, unless HIV medications are not tolerated due to the underlying liver disease. If antiretroviral therapy is not indicated or is stabilized, the HIV-HCV coinfecting patient is then evaluated for HCV treatment. Lower CD4 cells increase the speed of liver damage. Since HCV therapy causes the absolute number of CD4 cells to drop, it is helpful to have a cushion of CD4 cells to avoid risk of serious infections. (The CD4 percentage does not change on HCV therapy and will be used to monitor your HIV while on HCV therapy.) Persons with higher CD4 counts have better responses to HCV therapy. A medical provider may wait until a person's CD4 cells are >350 cells/mL. However, treatment decisions will also be based on the severity of the liver disease.

The liver biopsy result will be used to guide the management of your HCV treatment. HCV therapy is strongly advised in patients with advanced stages of fibrosis on the biopsy since there is a greater risk of complications from liver disease. Treatment for earlier stages of fibrosis with pegylated interferon and ribavirin does work better but might be deferred especially if infection occurred a long time ago since this means their rate of progression is slow. The most advanced scarring of the liver is called cirrhosis but it may take over 30 years to develop from the time of infection. Conversely, early liver disease may be treated if the patient is genotype 2 or 3 since the cure rates are high, if the patient is young, symptomatic or HIV positive. HIV accelerates HCV progression and can cause liver damage and scarring to be worse. CD4 cell increases can be blunted by HCV. It is not clear what impact HCV has on HIV but the risk of liver toxicity from HIV medications seem to be greater in persons infected with HCV.

The primary goal of HCV treatment is to cure HCV. A person is considered cured of HCV if the HCV viral load is cleared in the blood 6 months after completing treatment. The treatment duration is generally for 24 to 48 weeks depending on the

type of HCV you have and whether you also have HIV. If you have HIV, your medical provider may continue HCV therapy longer than if you did not have HIV.

By 12 weeks on therapy, your health care provider will know whether you will cure your HCV. However, therapy may be continued even if it is unlikely that you will cure your virus because there are other benefits of HCV treatment. HCV therapy can also improve the health of the liver, delay the progression of the disease, decrease inflammation and scarring of the liver, and decrease the risk of life threatening complications of liver disease including liver cancer.

If you and your medical provider decide that HCV therapy can be delayed, you should be monitored closely. A liver biopsy may be repeated in 3-5 years for the HCV mono-infected patient and earlier for the HIV-HCV infected patient since fibrosis is accelerated in HIV positive patients.

The HCV treatment response rates for someone without HIV is approximately 40% in genotype 1 and 80% in genotypes 2 and 3. There is a decreased response to HCV therapies in HIV positive patients compared to those without HIV. Recent data in HIV-HCV coinfecting patients showed response rates of 14% to 29% in genotype 1 and 43% to 62% in genotypes 2 and 3. Each of the available studies in HIV-HCV coinfecting patients had patients with different baseline characteristics, different dosages of HCV medications used and different discontinuation rates. Therefore, response rates in the studies cannot fairly be compared. However, although the response rates may be lower in the coinfecting patient, there is still the possibility of cure. Combination pegylated interferon and ribavirin was shown to be more effective than pegylated interferon alone or non-pegylated interferon with ribavirin.

Just like in HIV, adherence to HCV medications matters! Patients who maintain higher doses of their medications during treatment are more likely to clear their virus. It is better for the optimal success of your treatment to treat side effects and use growth factors like erythropoietin (Procrit or EPO) to improve anemia and granulocyte colony stimulating factor to correct neutropenia than to reduce the dose of your HCV medications. If you are having trouble taking the medications, let your medical provider know. He or she is there to help you stay on your HCV therapy.

Long term maintenance therapy with low dose pegylated interferon can be considered in patients who do not cure their virus with HCV therapy and have very advanced fibrosis on their liver biopsy. Other interferon therapies, for example interferon alfacon-1, may also be considered in patients who do not respond to pegylated interferon/ribavirin therapy. Some providers may consider switching to one of these alternatives when it is established that the patient will not achieve a cure with pegylated interferon/ribavirin, possibly even at 12 weeks.

There can be many side effects associated with HCV therapy. HIV and HCV therapies should not be started simultaneously so that your medical provider can better figure out which medication is the cause of any side effects. Your medical team will need to see you and check your blood frequently to be certain that you are doing well on the medications. In this newsletter you will find a side effect management chart with tips. Always talk to your medical provider before starting over-the-counter medications, diet modifications or exercise regimens. Also, find out how to access emergency help after clinic hours and

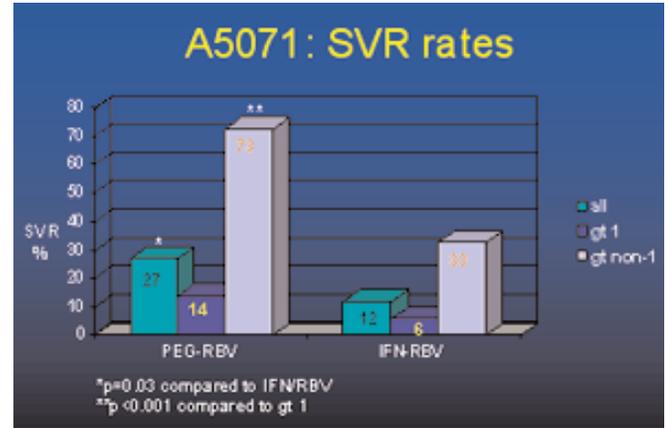
Three Coinfection Studies: RIBAVIC (PegIntron+ribavirin, n=418); APRICOT (Pegasys+ribavirin, n=868); ACTG 5071 (Pegasys+ribavirin, n=133)

The final results of these 3 studies were presented at the 2004 Retrovirus Conference. Ribavirin dosing was 800 mg a day in both APRICOT & RIBAVIC. But in ACTG 5071 induction dosing was used as patients started the study with 600 mg of ribavirin and dose escalated over the first 8 weeks, and this may have reduced the Sustained Viral Response Rates.

Sustained Viral Response (SVR) in ACTG 5071: Overall 27%; 73% for genotype 2/3; 14% for genotype 1.

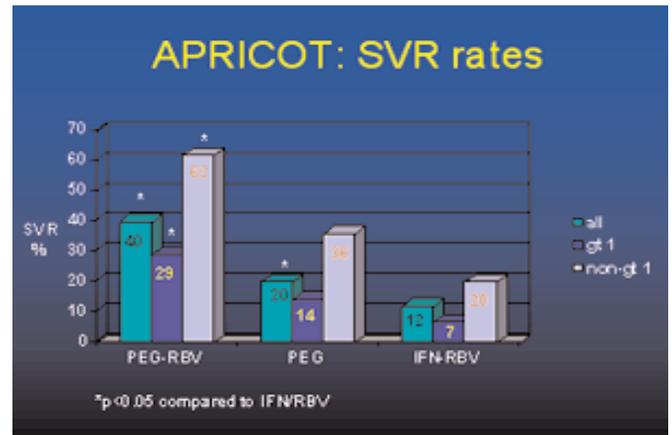
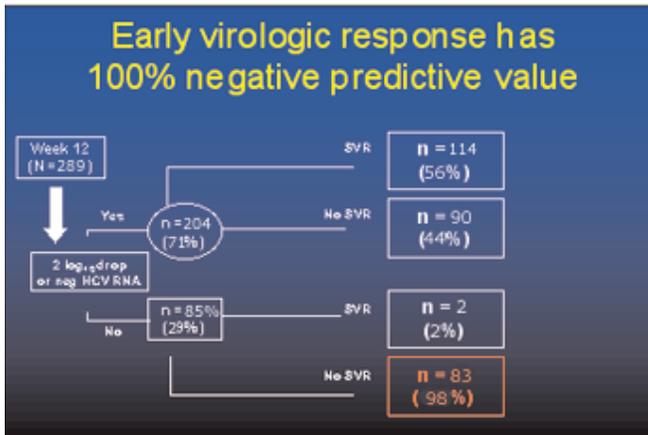
Comparison of baseline characteristics between studies

	ACTG 5071	APRICOT	RIBAVIC
Ethnic: C/AA	48%/33%	78%/10%	NR
GI 1-4 / 2-3	78%/22%	61%/39%	58%/42%
Log HCV RNA	6.2	6.7	5.9
Bridging or cirrhosis	44%	16%	40%
CD4	444-492	520-542	514
HAART, %	86%	84%	82%



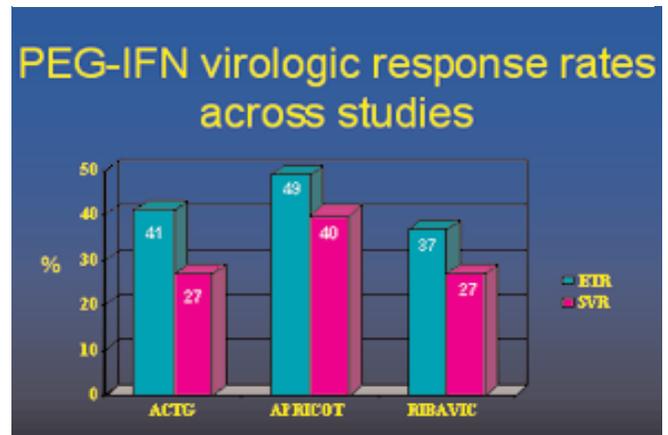
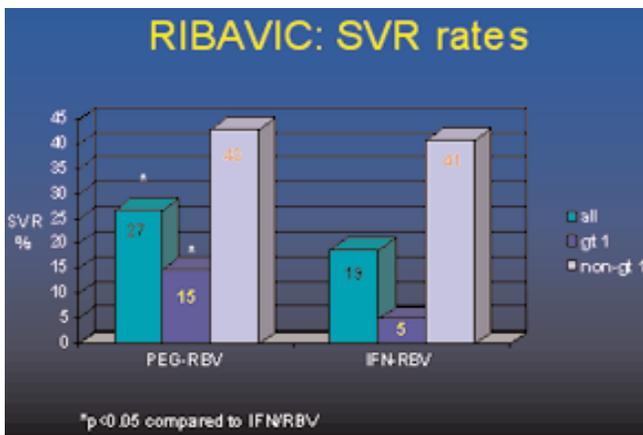
Early Viral Response (EVR) by Week 12 in Apricot. 98% of patients without EVR by week 12 did not achieve SVR; 56% who had EVR had SVR.

Apricot SVRs: for Pegasys+ribavirin- overall 40%; 29% for genotype 1; 62% for genotype 2/3



Ribaviric SVRs: for PegIntron+ribavirin- overall 27%; genotype 1- 15%; genotype 2/3- 43%.

Summary of all 3 studies: End of treatment Response (ETR) & SVR



on the weekends.

Other ways to help your liver if you have HCV is to avoid alcohol since it significantly accelerates liver scarring and progression of HCV. Get vaccinated for Hepatitis A and B if your blood does not show that you are already immune to these diseases. If you clear your HCV either spontaneously or with medication, you can get HCV again. Know how to protect yourself from being exposed to HCV again.

Whether or not you take medications for your HCV, stay connected to your medical team. Keep your medical appointments and be honest with your medical providers. Tell them how you are feeling and ask any questions you have. It is always best to know that you have done everything possible to keep you and your liver healthy.

Side Effect Management of Hepatitis C Treatment

Heather Wilantewicz, RPA-C
Director of Clinical Services
The PATH Center
The Brooklyn Hospital Center

Treatment for Hepatitis C Virus (HCV) consists of combination therapy with weekly pegylated interferon injections and daily ribavirin pills. The primary goal of HCV treatment is to cure HCV. However, HCV therapy can also improve the health of the liver, delay the progression of the disease, decrease inflammation and scarring of the liver, and decrease the risk of life threatening complications of liver disease including liver cancer.

Every medication has side effects. Pegylated interferon and ribavirin can have side effects and sometimes may be difficult to tolerate. Not everyone taking HCV medications will experience the same side effects and to the same degree. You will not experience every side effect listed in the package insert that comes with your medication. Companies are required to list every adverse effect reported on their drugs even if it is uncommon.

Interferon side effects can include "flu-like" symptoms such as fever, chills, headaches, muscle or joint aches, tiredness and weakness. Mood changes, depression, and weight loss can occur. Interferon can cause decreases in white blood cells (which help fight infection), and ribavirin can destroy red blood cells (which carry oxygen to the cells). The side effects related to HCV therapy are the most severe after the very first injection and usually do get better. Most adverse effects are reversible after the treatment is discontinued. Women and female partners of men on HCV treatment should not get pregnant while on therapy and for six months after therapy since ribavirin can cause serious birth defects.

Usually, the side effects of peginterferon and ribavirin are manageable. You will want to find a medical provider who is an expert in treating HCV and comfortable managing medication side effects. Ask about the side effects, anticipate them and learn how to manage - even prevent - them before they occur. Studies have shown that patients have higher rates of

suppressing HCV if they are adherent to their medication. Managing your side effects will help you adhere to the medication. Adherence improves response to therapy. Always be honest with your medical provider about your side effects. Your health care providers are there to help you stay on your HCV treatment. Be a partner in your care. Your side effects may be a sign of something serious or they may be easily treatable if your medical provider knows about them. Be sure to keep all of your appointments for blood tests and medical follow-up. If you think you are having a serious side effect, see your medical provider right away. Your medical provider can only help you if (s)he knows that there is a problem.

Some general recommendations for decreasing side effects from interferon therapy include administering your injections in the evening or before bed so that you sleep through some of the side effects. Take a pain medication like acetaminophen (no more than 2 grams per day) or a nonsteroidal anti-inflammatory drug (NSAID) like ibuprofen 1 hour prior to the injection and repeat 4-6 hours later if needed. Choose a day of the week to take the injection in which you do not have a lot to do the next day or two. If you go to work or a treatment program Monday through Friday, then take the injection on Friday night so that you have the weekend to feel better. Do not over extend yourself the day after your interferon injection. Plan lighter activities and take time to rest.

Adequate fluid intake is critical during HCV therapy. WATER, WATER, WATER is the number one way to decrease the common side effects associated with HCV therapy. Those who are most uncomfortable during therapy are usually not drinking enough water each day. Dehydration can occur during HCV therapy due to water loss from fever, chills, nausea/vomiting, poor appetite and decreased water intake. Follow this formula: Weight in pounds / 2 = ounces of water to drink each day. For example, if you are 130 pounds, you should drink 65 ounces of water each day (130 / 2 = 65). You could fill a 2 liter bottle with water in the beginning of the day and be certain that you drink all of the water from it by the end of the day. Carry a water bottle with you throughout the day so that water is easily accessible. Avoid caffeine which is present in tea, coffee and cola. Loss of appetite and weight loss can occur while on HCV therapy. Eat a nutritious diet with enough calories to maintain your weight. Prepare meals on days you feel like cooking and freeze them for days when you don't. Alcohol should be avoided since it can cause more damage to your liver.

Below is a chart with other suggestions for managing side effects related to HCV therapy. Always speak to your medical provider before starting any over-the-counter medications, diet modifications or exercise regimens. Starting HCV treatment does not commit you to staying on therapy for 48 weeks or more. It means you are just committing to try therapy. You can always stop the treatment if you have difficulty. In most cases, HCV medication is not forever. It is for a limited time in your life. At least you can then say you tried to do something to cure your HCV and improve the health of your liver. Talk to other people going through treatment or who have been through it. Surround yourself with supportive and motivating people. Be an advocate for yourself and take charge of your health. You can do it!

Condition	Treatment (For every condition, the Health Care Provider (HCP) should always rule out other serious medical causes.)
Flu-like Symptoms	Rule out infections and other causes. Maintain adequate hydration and electrolyte intake. Avoid caffeine. Drink more water and avoid caffeine. Administer injections at bedtime. Take a pain medicine such as acetaminophen (Tylenol) or a non-steroidal anti-inflammatory drug (NSAID) (e.g., Advil, Aleve, Motrin) 1 hour before the interferon injection and 4-6 hours later if needed. Try warm compresses or soaks for muscle/joint aches. Use cooling packs if fever. Wrap yourself in blankets if chills.
Headaches	Always tell HCP about headaches so that (s)he can rule out other medical conditions (e.g. anemia, dental or vision problems, hypertension, other medications, sinusitis etc.). If the headache is related to HCV therapy, ask your HCP to recommend a pain medicine such as acetaminophen (Tylenol) or non-steroidal anti-inflammatory drug (NSAID) (e.g., Advil, Aleve, Motrin) to take 1 hour before the interferon injection and 4-6 hours later if needed. Keep hydrated. Limit caffeine. Apply cold compresses to painful location. Use heating pad to relax neck or shoulder muscles. Avoid alcohol. Eliminate stress and worry.
Depression Irritability	Talk to your HCP about your feelings. If you have a history of depression, your HCP might start an anti-depressant before starting HCV treatment. Consider counseling and support groups. Try mild to moderate exercise. Increase fluid intake and avoid caffeine. Avoid stressful situations if possible. Talk to others who have been through treatment. Learn relaxation strategies (music, visual imagery, walking etc.) and get enough rest.
Neutropenia	Neutropenia is a decrease in a type of white blood cells that fights infection. Cause should be identified. If related to HCV therapy, injections of granulocyte colony-stimulating factor (G-CSF) can help maintain normal neutrophil counts and will allow you to tolerate higher doses of HCV medications and improve your response to HCV therapy.
Anemia	Anemia means decreased red blood cells. Red blood cells carry oxygen to the cells. If you are anemic, you may feel tired. Treatment is based on cause. Causes of anemia include medications, chronic diseases and deficiencies in iron, vitamins, or erythropoietin (a kidney hormone that stimulates the bone marrow to make red blood cells). The major side effect associated with ribavirin is anemia which can occur quickly. Weekly injections of erythropoietin may be needed during HCV therapy. Correcting anemia can improve energy and quality of life and allow you to tolerate higher doses of HCV medications and improve your response to HCV therapy.
Fatigue Weakness	Your HCP should check for low testosterone, poor nutrition, weight changes, depression, thyroid problems, sleep disorders, stress, pain, vitamin deficiencies, other sedative medications (e.g., drowsy antihistamines) and anemia (see anemia section above). Rest and take a nap if necessary. Conserve your energy especially on the day of and after the injection. Decrease alcohol and other sedatives. Exercise, water and good nutrition can give you energy. May need pharmacologic intervention.
Difficulty Sleeping	Check for depression. Allow 1 hour before bedtime to relax and avoid stressors. Go to sleep at night and wake up in the morning at the same time each day. Use bed only for sleeping or sex (e.g., not TV watching, reading etc.). Limit napping, caffeine, fluids at bedtime and late night meals. Get regular exercise. Avoid alcohol use.
Anorexia	Treat depression, nausea or taste changes. Eat small frequent meals. Maintain good oral hygiene. Marinate foods and use spices. Prepare meals ahead of time and freeze for days when you do not feel like preparing food.
Nausea	Rule out other causes (e.g., acid reflux, pregnancy). Be sure to drink enough water. Eat small frequent meals and eat slowly. Avoid acidic, spicy, fried and greasy foods. Eat cool or room temperature foods. Eat dry, bland foods like rice, toast or crackers. Try drinking flat ginger ale. Cut a lemon and smell the slices to lessen nausea. Avoid foods with strong odors (e.g. coffee). Keep a window open or microwave foods when preparing meals to limit food odors. Rest and elevate body 1 hour after meals. Stop smoking. Consider acupuncture. Wear loose clothes. Ask your HCP about anti-nausea medications.
Dry Mouth	Drink plenty of fluids. Eat softer moister foods. Use gravies and sauces to moisten foods. Try sugarless candy. If taste is metallic, avoid food/drinks in metal containers and use plastic utensils instead of metal. Practice good dental hygiene: floss and brush your teeth to avoid dental problems.
Taste Changes	Use plastic utensils instead of metal. Eat foods cold or at room temperature. Rinse mouth regularly and keep oral hygiene clean. Try sugarless candy. Hide taste changes with tart beverages and condiments. Avoid tobacco. Use seasonings/marinades/spices/sauces/gravies/fruit sauces
Weight Loss	You can lose weight on HCV therapy but your HCP will also check for infections, thyroid disease, depression and other medical conditions. Control any nausea, diarrhea and taste changes. Eat small, frequent meals. Prepare meals ahead of time. Consult a registered dietician.
Hair Loss or Hair Thinning	Get your thyroid panel checked. Use mild shampoos and conditioners, soft brushes and wide-tooth combs. Avoid daily washing, hair dryers, tight braiding or ponytails, hair dyes, curling irons and harsh chemicals/dyes or permanents. Scarves, hats and short hairstyles will make hair loss less noticeable.
Injection Site Reactions	Maintain sterile technique. Apply ice to the injection site prior to the injection to numb area if necessary. Rotate your injection sites. Let the alcohol dry after swabbing vial or injection site. Inject the medication at room temperature. Oral analgesics 1 hour prior to injection. Application of cool or warm compresses to site before and/or after injection
Itchiness	Your HCP will rule out other medical conditions and allergic reactions. Rotate the injection sites. Keep hydrated. Take lukewarm or cool bath/showers. Use oatmeal soaps and soaks. Pat skin dry instead of rubbing. Your HCP may recommend steroid creams or oral antihistamines. Use non-alcohol based and non-fragrant creams, lotions, soaps, and laundry detergents.
Constipation	Interferon can slow down the GI tract but other medical conditions should also be ruled out. Check with your HCP if other medications that you are taking can worsen constipation (e.g. methadone, opioids, iron supplementation, antidepressants). Drink extra water, exercise and increase fiber in your diet. Ask your HCP about stool softener medication.
Diarrhea	Your HCP will need to rule out other medications, certain foods/fluids, stress, anxiety, lactose, recent antibiotic use, infections, and overdose of Vitamin C. Eat small frequent meals. Decrease caffeine and fatty and fried foods. Increase fiber in diet. Your provider may need to send stool to the lab to rule out infections or refer you to a GI specialist. Your HCP may recommend anti-diarrheal medications, glutamine, oat bran or calcium supplements. Keep hydrated and avoid dehydration.
	Always consult your Health Care Provider before starting any over the counter medications, diet modifications or exercise regimens.

Update: New Drugs in Development for Hepatitis C

Jules Levin, Executive Director, NATAP



The two most interesting types of drugs researchers are trying to find are polymerase inhibitors and HCV protease inhibitors. These appear to be the easiest types of drugs to develop. BILN-2061 was an HCV protease inhibitor that received much attention a year ago because researchers at

Boehringer Ingelheim, the company developing this drug, reported very potent reductions in HCV viral load in a study in which HCV+ patients received the drug for a few days. These findings established that HCV protease inhibitors are possible to create and develop. Unfortunately, development of BILN-2061 was stopped due to finding toxicity in animals. Still, the company has other drugs for HCV it is developing. Several drug companies are researching inhibitors of the polymerase enzyme, which is a popular target for new drugs. Although research for new HCV drugs is receiving much attention and there are numerous research programs ongoing at large and small pharmaceutical companies, bear in mind it appears that the availability of any new HCV drugs will not occur for at least 4-5 years. Even then pegylated interferon will apparently still have to be used in a treatment regimen. Therefore, proper evaluation of the stage of liver disease is crucial in deciding whether a patient can wait for new drugs. Undue delay in starting treatment can result in serious complications of liver disease and cirrhosis. The following is an update on the most promising developments in the search for new drugs.

Schering Plough Hepatitis C Protease Inhibitor, SCH7

Schering Plough researchers discussed preliminary results from early study of this protease inhibitor for HCV at the AASLD Conference in late 2003. The candidate Schering Plough is currently studying in Phase I is SCH7, but they presented study results from the sister drug SCH6, which showed potent inhibition of HCV RNA replication in vitro (laboratory test tube). SCH6 was non-toxic to transfected Huh-7 cells for at least 6 weeks and for concentrations up to 200 nM. Analysis of potential resistant variants is ongoing.

Francesco Negro, a researcher from Geneva Switzerland, along with Schering Plough researchers, used multiple procedures to assess the antiviral activity of this novel protease inhibitor known as SCH6 in a standard cell line (Huh-7 hepatoma cells) that was infected with HCV. After a 72-hour incubation period with varying concentrations of SCH6, viral transcription and protein expression were measured by real-time polymerase chain reaction, or PCR (by TaqMan), quantitative in situ hybridization, immunoblot and indirect immunofluorescence.

HCV replication and expression were effectively inhibited by SCH6, which reached its peak activity at 100 nM, as consistently shown by all procedures used. At these concentrations and for these lengths of incubation, SCH6 did not appear to

induce cytotoxic morphological changes or apoptosis (cell death).

Researchers noted that while HCV protease inhibitors show promise in early stage development, much additional work will be required before this class of compounds becomes available to patients. Human study of this drug is ongoing.

New HCV Protease Inhibitor Study Planned for 2004 4th Quarter

"Vertex Pharmaceuticals Announces Initiation of First Human Clinical Trial for VX-950, an Investigational Oral Protease Inhibitor for the Treatment of Hepatitis C"

Vertex Pharmaceuticals very recently announced it has successfully completed the dosing portion of a Phase Ia clinical trial for VX-950, an investigational oral protease inhibitor for the treatment of hepatitis C virus (HCV) infection. The study, involving 35 healthy volunteers and conducted in Europe, was designed to assess safety, tolerability and pharmacokinetics in escalating, single doses of VX-950. Based on the results from this study and preclinical studies, the Company expects to begin a Phase Ib clinical study of VX-950 in HCV-infected patients by the end of 2004. This placebo-controlled trial will be designed to evaluate the safety, tolerability, and pharmacokinetics of up to 14 days of dosing with VX-950 in both healthy volunteers and HCV-infected patients.

Vertex officials reported that in the Phase Ia study, single doses ranging from 25 mg to 1250 mg were administered. No dose-limiting toxicities were identified, and a maximum tolerated dose was not reached. However, blood concentrations of VX-950 were observed that exceeded the concentration known to demonstrate potent antiviral activity in preclinical laboratory experiments, and at certain dose levels these target concentrations were maintained for more than 12 hours.

Preclinical studies have shown that VX-950 significantly reduces levels of HCV RNA in both an in vitro replicon system and infectious virus assays. At a scientific conference in October 2003, Vertex scientists reported that VX-950 reduced HCV RNA 10,000-fold (4 log₁₀) in nine days in an in vitro replicon assay (in laboratory test tube). HCV viral load was reduced by 3-5 logs in vitro as monotherapy, and when combined with interferon the viral load was reduced more than with VX-950 alone. HCV RNA was cleared by VX-950 within days and no viral rebound was observed after withdrawal of the inhibitor. Monotherapy and interferon combination studies are planned.

Preclinical pharmacokinetic studies have indicated that VX-950 is orally bioavailable and achieves excellent exposure in the liver, the target organ for HCV treatment. The initiation of clinical testing of VX-950 represents a first step towards establishing the safety and tolerability in humans.

NM283: New Oral HCV Drug, Polymerase Inhibitor

"Phase I/II Dose Escalation Trial Assessing Tolerance, Pharmacokinetics and Antiviral Activity of NM283, a novel Antiviral Treatment for Hepatitis C"

Eliot Godofsky, (University of South Florida, Tampa), report-

ed on NM283, a new HCV drug (polymerase inhibitor), and the initial clinical study results at the DDW (Digestive Disease Week) Conference in May 2004. NM283 is being developed by Idenix, a pharmaceutical company based in Cambridge, Mass.

NM283 is orally administered and this is the first study conducted in HCV-infected patients. About 80 patients were studied with various doses. Using the highest dose regimen HCV viral load was reduced by a mean 1.1 log after 15 days of dosing. Patients were all genotype 1 and mostly interferon failures. Overall the drug appeared safe and tolerable. GI side effects were seen but were transient. The next planned study is a 4-week combination study with peginterferon.

Godofsky said in his talk that >800,000 cases of end-stage hepatitis C are expected in the USA in the coming decade; similar trend in Europe. We need high SVR rates with limited treatment duration, particularly in genotype 1 with >70% in the USA being genotype 1 and 60% in Europe. We need oral, safe and well-tolerated medicines with treatment for patients with decompensated cirrhosis.

In previously conducted study, NM283 inhibited HCV-1 replication in chronically infected chimpanzees by mean 1.05 log. 5 chimpanzees who were chronically infected with HCV-1 received oral treatment for 7 days once daily, 3 treatment arms: placebo (1 animal); NM283 8.3 mg/kg/day (7 animals); higher dose NM283 16.6 mg/kg/day (2 animals). Serum HCV RNA was quantified by Roche Amplicor PCR. HCV RNA was reduced by 0.83 log (low dose) and 1.05 log (high dose); no change in placebo chimp.

Godofsky's study was the first human dose escalation trial of this drug. The study objective was to evaluate safety, antiviral activity and pharmacokinetics of the drug during 15-day treatment and 2 week post-treatment follow-up. The patients were adults with chronic HCV; HCV genotype 1; interferon failures or treatment-naïve; compensated liver disease, no cirrhosis.

Dosing levels were 50-800 mg/day; each dosing group of 12 eligible patients randomized 10:2 to NM283 vs placebo. The study was held at 6 US sites.

Characteristics of patients: age 47-52; 60-70% men; 90% Caucasian; 90% interferon failures; HCV RNA (viral load) – average of 6.6 log IU/mL (this is a high viral load); average ALT – 64 units/mL; patient group 6 was dose escalated from 100 to 800 mg; group 7 was escalated from 400 to 800 mg + antiemetic (for GI upset).

Viral Load Reductions at Day 15

--The placebo group had no reduction.

--The dose escalation group 400 to 800 mg + antiemetic had average viral load reduction of 1.1 log.

--The group escalated from 100 to 400 had reduction of 0.8 log.

--In patient group 7, individual patient HCV RNA reductions ranged from 0.68 to 1.94 log. One patient had reduction of

1.94 log; 2nd patient's viral load declined by 1.37 log; three patients had 1 to 1.2 log reductions.

Safety & Tolerance

Godofsky reported clinical safety satisfactory overall: no serious adverse events or dose limiting toxicities; all 68 compliant patients completed treatment; no grade 3 or 4 lab abnormalities during treatment; no pattern of lab abnormalities.

GI side effects in some patients (typically transient nausea; total of 5 patients with vomiting): seen primarily at doses \geq 400 mg/day; 23 of 26 nausea events rated "mild", 3 "moderate"; most with onset in first 2 days; <1 day duration in 62% of affected patients; 5/14 (36%) placebo patients with miscellaneous GI complaints. Godofsky said overall side effects favorable compared to current treatment.

Godofsky concluded: there was consistent antiviral activity in patients, 87% of whom previously failed interferon; increased antiviral activity with each higher dose: HCV RNA reductions after 15 days treatment was -0.15 to 1.1 log IU/mL in completed patient groups; 1.1 log viral load reduction equals 92% viral load reduction in 2 weeks; in highest dose group, 9/9 previous IFN failures exhibited HCV RNA responses (0.7-1.9 log: 79-99% HCV RNA reductions in individual patients over 2 weeks); 800 mg/day cohort ongoing; overall safety satisfactory: no dose limiting toxicities, transient nausea & vomiting in some patients, all compliant patients completed treatment. The next planned study is a 4-week combination trial of NM283 and peginterferon.

Viramidine Appears to Reduce Incidence & Severity of Ribavirin Associated Anemia

"Clinical Study of Viramidine in Treatment of Hepatitis C Supports Red Blood Cell-Sparing Mechanisms of Action"

Summary: Ribavirin is associated with causing anemia in HCV+ receiving interferon/ribavirin therapy for HCV. It would be very helpful for patients if they could eliminate or reduce anemia, which can cause difficult fatigue. Studies reported recently show preliminary results that Viramidine may be less likely to cause anemia and if it occurs the anemia may be less severe compared to ribavirin. The study results only report viral load (HCV RNA) results for 24 weeks therapy. Phase III studies are ongoing and will show if viral load responses are equal for Viramidine compared to ribavirin. Viramidine is a pro-drug for ribavirin. This drug is being developed by Valeant Pharmaceuticals.

Sanjeev Arora (University of New Mexico) reported study results at the Digestive Disease Week (DDW) Conference May 2004 in New Orleans, LA. Pegylated interferon plus ribavirin (RBV) is the standard of care for therapy for the hepatitis C virus. Ribavirin are pills taken twice daily and is associated with anemia. During the first 4 weeks of combination therapy for HCV, hemoglobin (Hb) levels decrease an average of 2 to 3 g/dL and 10% to 13% of patients experience a decrease in Hb to <10 g/dL. About 25% of patients need to reduce dose of RBV due to anemia. It's difficult to predict who will develop anemia. Dose reduction of RBV may lead to decrease in sustained viral response, particularly during the

first 12 weeks after initiating peginterferon/RBV therapy.

RBV concentrates in red blood cells (RBCs) at a 100-fold higher concentration than in plasma. Uptake occurs via a NBTI-sensitive "es" nucleotide transporter. RBV is trapped in RBCs where it undergoes irreversible intracellular phosphorylation to RBV-triphosphate. Accumulation continues due to insufficient purine 5'-nucleosidase (phosphatase) activity in anucleated RBC.

High levels of RBV compete for phosphorylation enzymes resulting in depletion of intracellular ATP. Low levels of ATP in RBC lead to impaired anti-oxidant defense mechanisms, reduced red cell survival and anemia. Administration of antioxidants may not prevent RBV-induced anemia.

Pre-clinical studies have suggested Viramidine, a pro-drug of ribavirin, yields higher liver drug levels than ribavirin, with a corresponding reduction in drug concentrations in plasma and red blood cell (RBC). To test the hypothesis that viramidine is associated with less hemolytic anemia than ribavirin, researchers looked at hemoglobin reductions and ribavirin levels in RBCs in an ongoing dose ranging clinical study of viramidine as a part of combination therapy for hepatitis C.

Studies in monkeys of 10 mg/kg daily oral dosing found Viramidine had 50% lower levels in RBCs compared to RBV and 3 times greater levels in the liver than RBV.

The study randomized 180 treatment-naive patients in a 1:1 ratio to receive (Pegasys) peginterferon alfa-2a 180 ug/wk SC plus viramidine 400 (N=47), 600 (N=43), or 800 (N=45) mg BID (twice daily) or ribavirin 1000/1200 mg daily (N=45).

HCV RNA reductions were similar in the two groups at week 24 of therapy. So Viramidine did not appear to result in less reductions in HCV viral load than RBV after 24 weeks of therapy but 48 weeks and 72 weeks sustained viral load results are awaited to confirm efficacy of Viramidine.

Blood samples obtained during the study were evaluated for ribavirin Cmin concentrations in RBCs at weeks 4 and 12. Cmin is the levels of ribavirin seen at the end of the dosing period.

The mean ribavirin Cmin concentration in RBCs following 4 weeks of treatment with viramidine 1200 mg/day was 126 ug/mL compared with 246 ug/mL for the ribavirin treated group.

After 12 weeks of treatment, the mean RBC ribavirin Cmin was 159 ug/mL in patients who received viramidine 1200 mg/day compared to 235 ug/mL in ribavirin-treated patients. After 4 weeks RBV Cmin was 250 ng/ml for RBV compared to 135 ng/ml for Viramidine.

In phase 2 trials anemia (Hb <10 g/dL) incidence was 7% in patients receiving 800 mg Viramidine BID and 0% for patients receiving 400 or 600 mg BID Viramidine compared to 24% for patients receiving 1000/1200 mg RBV. Mean Hb declined by

about 4 g/dL for patients taking RBV compared to --2.5 to 3 g/dL for patients taking the 3 doses of Viramidine over 24 week period following initiation of HCV therapy. Investigators reported a smaller proportion of patients who received the highest doses of viramidine had hemoglobin ≥ 2.5 g/dL decrease from baseline (48% versus 82%) when compared with ribavirin-treated patients. At EASL Conference in April 2004 study investigators reported 67% of patients receiving 800 mg BID Viramidine had ≥ 2.5 g/dL Hb drop and/or <10 g/dL during 24 weeks compared to 82% receiving RBV 1000/1200 mg daily (P>0.05), 51% for Viramidine 600 mg BID and 45% for Viramidine 400 mg BID. Of note at EASL investigators reported incidence of patient-reported adverse events, and 33% reported fatigue for patients receiving 800 mg Viramidine, 33% by patients receiving 600 mg Viramidine compared to 31% for patients receiving RBV 1000/1200 mg BID. Depression rates were 18% for 800mg Viramidine, 9% for 600 mg dose of Viramidine vs 22% for RBV. Other commonly reported side effects were reported at similar rates of incidence as well. The percentages of patients reporting rigors and irritability were less at the 600 mg Viramidine dose than the RBV dose 1000/1200mg/daily.

The study investigators concluded that the cascade of events that lead to hemolysis begins with the preferential uptake of RBV into RBCs. Viramidine is a liver targeting, pro-drug of RBV that does not significantly accumulate in the RBC. The lower concentration of Viramidine-derived RBV in plasma correlates with significantly less decline in Hb. In phase II clinical study, Viramidine at doses of 400 mg BID and 600 mg BID at 24 weeks resulted in no instances of anemia (Hb <10 g/dL) and no dose reductions due to anemia. Based on 24 week interim data, Viramidine decreases RBC exposure to RBV, resulting in less anemia and comparable antiviral response. Results from ongoing phase III studies are awaited.

Hepatitis C Review Issue No. 3 Fall 2004

Published & Edited by: Jules Levin, Executive Director, NATAP

Contributions by: Heather Wilantewicz, RPA-C

Layout and Production: Jessie Gibson

For additional copies of Hepatitis C Review contact NATAP.

National AIDS Treatment Advocacy Project (NATAP)

580 Broadway, Suite 1010

New York, NY 10012

Tel: (212) 219-0106

Fax: (212) 219-8473

Email: info@natap.org

Website: www.natap.org

Website: www.hepcadvocacy.org