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Pegasys Plus Ribavirin - An Analysis: Will this Combination Become the Next Standard of Care?

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As I wrote in October 2001 for the HCV Advocate, every person affected by hepatitis C, including me, has been waiting for many years for the approval of the pegylated interferons in combination with ribavirin. There were four reasons promised for a long time suggesting that this new combination would be a major advance over the then standard of care, Rebetron (standard interferon alpha2b plus ribavirin). Patients and healthcare providers dealing with hepatitis C were hoping for increased sustained virologic response (SVR). SVR means HCV RNA negative at six months after treatment. Secondly, the pegylated interferon would show a further improvement in liver histology (the health of the liver) and a slowing of the progression to cirrhosis. Thirdly, the new therapy would be easier to tolerate and have fewer side effects,

and finally, it would be more convenient and easier to administer.

When Peg Intron/Rebetol (pegylated interferon alfa 2b 1.5mcg plus ribavirin) was approved in 2001, I analyzed the package insert focusing on these four areas of hope for patients with hepatitis C. Now that Pegasys/Copegus (Roche's ribavirin) is approved, I will share with you a similar analysis of the Pegasys combination package insert that I have completed.

In regards to efficacy or effectiveness, the overall SVR for Pegasys 180µg plus Copegus 1000/1200mg in clinical trials ranged from 53% in the 801 trial published in September, 2002 in the NEJM, to 44% to 61% when compared to Rebetron in the 942 trial presented at EASL this year—which is the overall highest SVR ever reported in the treatment of hepatitis C. In pooled data from both trials, for patients

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with high viral load and HCV genotype 1 the SVR was 43% for Pegasys/Copegus, and for those patients with low viral load and HCV genotype 1, the SVR for Pegasys/Copegus was 56%. (In the 801 trial the SVR for genotype 1 was 44% for Pegasys/Copegus versus 36% for Rebetron, and the SVR for genotype 2-6 was 70% versus 59%. The 942 trial did not have Rebetron as a comparator.) The Pegasys/Copegus package insert confirms what we already have long suspected, and that is that genotype, age, degree of fibrosis and weight are all host factors affecting the overall sustained virologic response in the treatment of hepatitis C. In pooled data of the two trials, treatment responses were lower in patients older than 40 years (50% vs. 66%), in patients with cirrhosis (47% vs. 59%), and in patients weighing over 85kg (49% vs. 60%). Unfortunately, these host factors dominate the treatment pool in the United States, hence adding to treatment challenges.

The next area I analyzed was whether there was a histological improvement from the Pegasys component of therapy. This is especially important for those patients who do not clear the virus, but at least could have an improvement in liver health. The Pegasys/Copegus package insert is the first pegylated interferon to be indicated in patients with both compensated liver disease and histological evidence of cirrhosis (Child-Pugh Class A). This addition of cirrhotics to the indication is due to the mono cirrhotic trial which enrolled patients with a histological diagnosis of cirrhosis (78%) or bridging

fibrosis (22%) as well as the fact that the 942 combination trial had about 25% cirrhotics, which is considerably higher than the other pegylated phase III combination trials. The Pegasys/Copegus package insert states that there were similar reductions in inflammation across all treatment arms, and the fibrosis improvements listed in the mono Pegasys label were not recognized in the combination label for Pegasys/Coegus.

When I looked at the side effect profile of Pegasys/Copegus compared to that of Rebetron, I was pleasantly surprised. Across almost every type of annoying side effect having an impact on adherence, in clinical trials Pegasys/Copegus had a significantly lower percentage of side effects than Rebetron. The more common adverse events in the Pegasys/Copegus patients were myalgia: (muscle pain) - 40%, a 9% decrease compared to Rebetron; irritability/anxiety/nervousness - 33%, a 5% decrease compared to Rebetron; insomnia (inability to sleep) - 30%, a 7% decrease compared to Rebetron, and depression - 20%, an 8% decrease compared to Rebetron. It should be noted that side effect profiles in package inserts can be misleading because there is no severity scale which would record how often a patient experienced a side effect, or how severe it was. Keep in mind, though, that this theory would also hold for reported Rebetron side effects (as it was a head-to-head trial), so the difference in percentages from a trend perspective is accurate. Even with this in mind, the side effect profile of Pegasys/Copegus appears much easier to tolerate than that of Rebetron, and therefore is likely

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to have a positive

impact on a patient's ability to stay on therapy or be compliant with therapy.

The last benefit that we had come to expect from the pegylated interferon combination was ease of use and convenient dosing. A benefit that patients will have from Pegasys/Copegus is that they will only have to administer the interferon once per week, versus three times per week for Rebetron. Additionally there are other considerable benefits as it relates to ease of use and convenient dosing. Pegasys does not have to be weight based dosed as does Peg Intron so all patients get one dose, 180µg subcutaneously weekly. Pegasys also comes in a ready-to-use solution that needs to be refrigerated and there is no reconstitution; therefore the opportunity for patient error is very much reduced and the process obviously much simpler for the patient. Additionally, patients with genotype 2 and 3 only require a 24 week treatment duration and low dose ribavirin (800mg) when treated with Pegasys/Copegus.

The title of this article poses the question as to whether Pegasys/Copegus will become the next standard of care. For years the pegylated interferons have been hyped to be a major improvement over Rebetron for the four reasons I listed earlier—increased SVR, improved histology (liver health), improved tolerability and, lastly, convenience and ease of use. In prospective clinical trials Pegasys/Copegus, across all patient genotypes including cirrhotics, has demonstrated efficacy surpassing Rebetron especially in difficult to treat patient populations including genotype 1, high viral load and cirrhotics. Even though no fibrosis improvement data was listed in the combination package insert, Pegasys/Copegus is indicated in cirrhotics and has been widely studied in this population. Furthermore, the HALT-C trial should answer many of the remaining questions. Pegasys/Copegus has consistently demonstrated a tolerability profile better than that of Rebetron in both pivotal phase 3 trials, and lastly, what

could be more convenient than a ready to use solution, once a week and one dose for all?

Based upon what is available today I believe that Pegasys/Copegus will become the next standard of care—but a word of caution. There are still many patients who are going to have to be patient and wait for the first non-interferon based drug to come to market for the treatment of hepatitis C. Keep in mind that the results presented in the pegylated interferon package inserts are based on naïve patients and there are many hepatitis C patients awaiting treatment, including me, who are either multiple relapsers or non-responders, and for whom the results will not nearly be as favorable as for the naïve patient.

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Depression and HIV, Part 1

AIDSMeds.com

In the language of clinical psychology, depression is a syndrome, a cluster of emotional, physical and behavioral symptoms characterized by sadness, low self esteem, loss of pleasure, and, sometimes, difficulty functioning. If these problems persist over a period of time, cause real suffering, and interfere with the business and pleasure of daily life, you may have a clinical depression.

In everyday conversation, people say they are depressed when they are feeling unhappy, down, blue, sad, or hopeless. Almost everyone has experienced these emotions, and if you have HIV disease, you may have reason to be anxious or depressed at times. These feelings are just one part of everyday life for most people.

However, if the feelings are overwhelming or persistent, you may benefit from psychological evaluation and treatment. Depression of this type can be effectively reduced or even eliminated with (often relatively simple) treatment. Professional intervention in serious depression can reduce suffering and improve the quality of life.

What is the psychiatric definition of depression?

In the U.S. today, psychological symptoms are organized into diagnostic categories written by the American Psychiatric Association (APA) and currently known as DSM4 criteria. These categories are pragmatic constructs and do not capture the richness of mental and emotional life. They are useful in determining whether medication might reduce your symptoms and, if so, which medications

should be tried.

There are several sub-categories of depression. The most common are major depression and dysthymia.

Basic criteria for major depression are (literally) 1 symptom from column A and 4 symptoms from column B (see table), lasting for at least 2 weeks.

What other problems might I notice if I'm depressed? Besides the criteria listed above, you may experience some of the following problems if you are depressed:

- Criticizing, attacking, and berating yourself.
- Skipping days of work or not going to work.
- Inability to study or pursue serious intellectual or artistic interests.
- Loss of interest in sex.
- Avoiding friends or usual social activities, hobbies, or recreations.
- Inability to enjoy activities or events in which you normally take pleasure.
- Neglecting yourself physically (in terms of grooming and hygiene).
- Forgetfulness.
- Crying a lot or feel like crying without knowing why.
- Feeling irritable and getting into arguments easily.
- Increased and excessive use of alcohol or other recreational drugs.

One of the common symptoms of depression is a

Criteria for Major Depression

COLUMN A (MUST HAVE ONE OF THESE)	COLUMN B (MUST INCLUDE FOUR OF THESE)
<ul style="list-style-type: none"> • Feeling depressed (down, sad, blue, hopeless) most of the day and almost every day. It can evolve gradually over a few weeks or suddenly after great stress. • Loss of interest and pleasure in things that are usually interesting and pleasurable; this can be partial or complete. Some people may not be able to feel better no matter what the circumstances; others may periodically respond to positive things by feeling better. 	<ul style="list-style-type: none"> • Loss of appetite and/or weight loss without dieting or medical cause, increase in appetite and/or undesired weight gain. • Insomnia (waking up early and not being able to fall back asleep; difficulty falling asleep), or sleeping too much. • Being slowed down physically or mentally. You and other people notice that it takes you longer than usual to accomplish activities. • Being agitated (restless, can't sit still, pacing, wringing hands, rubbing head). • Fatigue; loss of energy. • Feeling excessively guilty or worthless. • Difficulty in concentrating. Feeling that your thinking is slowed down. Increased difficulty in making small decisions. • Persistent thoughts about death and/or suicide.

feeling of hopelessness.

If you are seriously depressed, you may feel that it is impossible to get help and that you will never feel better. You may feel that you have always been in this mental state. This hopelessness can lead to failure to get help. If friends comment on your depression or suggest that you get professional help, take them seriously.

Major depression can be a dangerous disorder. You may neglect to take necessary medication for HIV or skip doctor's appointments. You may take risks sexually that would be unacceptable to you in a non-depressed period of time. At its worst, it can lead to suicide.

If someone in your immediate family has had an episode of severe depression, studies indicate that you probably face an increased risk of developing this kind of depression.

I feel depressed most of the time, but I manage to function on a daily basis. Is there help for this kind of depression? Yes. Dysthymic disorder is a term used in psychiatry to describe an ongoing depression that may not be as severe as a major depressive disorder, but is chronic, often lasting for years—and, for some people, as long as they can remember.

The symptoms may be similar to that of major depressive disorder, but milder—that is, fewer and less severe symptoms. The diagnosis is usually made when the symptoms have lasted for at least two years.

Following are the American Psychiatric Association's DSM4 criteria for dysthymia: Criteria for Dysthymia. Feeling unhappy or "down" most of the time on most days, AND, while depressed, at least two of the following symptoms are present:

- Poor appetite or overeating.
- Difficulty sleeping or sleeping too much.
- Low energy or fatigue.
- Low self-esteem.
- Poor concentration or difficulty in making decisions.
- Feeling hopeless.
- Excessive use of alcohol or other recreational drugs.

People with dysthymia are able to work and generally conduct their lives, but often feel

irritable, are chronically unhappy with themselves, unable to enjoy things, and may feel that life is not very worthwhile.

When should I get help with depression? Major depressions often do get better on their own, but this can take at least six months or a year and some symptoms may persist for much longer. Adequate treatment can often shorten the period of time that you are suffering to a few weeks or less. Getting help may keep you from losing a job, a relationship or even your life.

Dysthymia can be lifelong, and many people who have episodes of major depression also suffer from dysthymia.

If depression is intense and interferes significantly with your daily life for a period of time (major depression), or if you are functioning adequately but feeling depressed for months at a time (dysthymia), you should seek help from a mental health professional. You should always seek help if you are suicidal or neglecting necessary medical care.

Can other medical problems or medications cause symptoms of depression? Yes. This is one of the reasons that your psychiatrist needs to take a careful history. For example, HIV+ men can have low testosterone levels which may cause decreased energy, loss of sexual desire, and feelings of depression. You can determine your testosterone level with a simple blood test, and should receive testosterone replacement if your level is abnormally low.

Sustiva, a drug used to treat HIV, can cause a variety of psychological side effects.

If your depression coincides with starting Sustiva and becomes severe or lasts more than a few weeks, you should consider switching to another anti-HIV drug to see if the depression improves.

In advanced symptomatic HIV disease, a number of opportunistic infections (OIs) as well as HIV itself can affect the brain so as to produce symptoms of depression. Antidepressant medication may still be indicated, but the underlying problem should be diagnosed first and treated if possible.

Being Alive, August/September 2002

Overcoming Peripheral Neuropathy

By Debra Boucaud-Obali

Michael, who stands at 5 feet 11 inches and 165 pounds, is a 35-year-old real estate agent from Queens who works out 4 or 5 times per week and practices very healthy eating habits. Except for the occasional flu, Michael has enjoyed good health, so he was at a loss to explain why suddenly, after each work day his leg muscles felt progressively weaker.

At first Michael thought he had suffered an injury during weight training but even after changing his work-out routine, the loss of sensation and pain in his lower extremities caused him to miss two days of work. Michael was forced to seek medical help and reluctantly went to his primary care physician.

After undergoing thorough physical and neurological examinations and a battery of diagnostic tests, Michael was shocked to learn he was positive for human immunodeficiency virus (HIV) and his neurological symptoms were due to acute inflammatory demyelinating polyneuropathy (IDP). IDP, a form of peripheral neuropathy, is a clinical complication of HIV disease and is sometimes the first clinical manifestation that a person is HIV-infected. Peripheral neuropathy is the most frequent neurological complication associated with HIV infection.

Understanding the Nervous System

Within the peripheral nervous system, there are three kinds of nerves: motor nerves, sensory nerves, and autonomic nerves. The motor nerves are responsible for voluntary movements such as picking up an object or jogging. Sensory nerves allow us to feel pain, vibrations and touch by transmitting signals from sensory receptors in the skin and other organs to the central nervous system. The autonomic nerves control involuntary functions like breathing, heartbeat, and digestion and they work automatically whether we are awake or asleep.

Most neuropathies affect all three types of nerves. Peripheral neuropathy describes disorders which occur from injury to the

peripheral nerves. These disorders can impair functional status, limit physical activity, and diminish quality of life.

There are at least six forms of HIV-associated peripheral neuropathy. Besides IDP, which Michael developed, a person with HIV disease may be diagnosed with distal symmetrical polyneuropathy (DSPN); progressive polyradiculopathy (PP); mononeuritis multiplex (MM); diffuse infiltrative lymphocytosis syndrome (DILS); or autonomic neuropathy.

Some Causes of Peripheral Neuropathy

Although Michael developed IDP, the most common form of peripheral neuropathy in people with HIV infection is DSPN. Unlike IDP which can occur at anytime during the course of HIV disease, DSPN occurs mainly with advanced immunosuppression and may also be secondary to the neurotoxic effects of antiretroviral medications such as didanosine (ddI), zalcitabine (ddC), and stavudine (d4T). Other medications which are considered neurotoxins and can cause DSPN include vincristine and cisplatin used to treat HIV-related lymphoma or Kaposi's sarcoma; and isoniazid used in the treatment of tuberculosis, especially when the person takes this drug without pyridoxine (vitamin B6) supplementation.

Besides medications, certain toxins such as lead, arsenic, mercury, thallium, organic solvents, and insecticides can cause peripheral neuropathy in persons infected with HIV.

Additionally, alcohol is directly toxic to nerves and alcohol abuse can be a major cause of peripheral neuropathy in someone with HIV. Unfortunately, some people increase their consumption of alcohol because of depression associated with the illness. These people could join support groups which can be helpful with management of alcoholism and depression related to HIV.

Peripheral neuropathy can also be caused by nutritional imbalance such as deficiencies of vitamins B12, B1 (thiamine), B6 (pyridoxine), or E. In people infected with HIV, this vitamin

deficiency can be due to poor diet or to inability to absorb nutrients from the stomach. Other reasons include poor appetite, diarrhea, pain and depression. Megadoses of vitamin B6 can also cause peripheral neuropathy.

Also considered at increased risk for developing peripheral neuropathy are those with HIV infection as well as other medical conditions. These conditions include diabetes, which is the most common known cause of peripheral neuropathy; some conditions where the immune system turns against the body causing autoimmune diseases such as Guillian-Barre syndrome, lupus, and rheumatoid arthritis; lung cancer; chronic renal failure; and hypothyroidism.

Symptoms of Peripheral Neuropathy

The symptoms experienced by those with HIV-related peripheral neuropathy depend on the types of nerves affected and their location, but the problem usually starts with weakness, numbness or pain.

For example, damage to the motor nerves can cause leg symptoms such as difficulty walking, running, tiring easily or stumbling. Sensory nerve damage can cause paresthesias such as numbness, tingling, pins and needles, burning, cold, sharp, deep stabs, or electric shocks. Or instead, one can also develop anesthesia, a lessening or absence of sensation, which can cause a person to burn or cut oneself and not know it.

Sensory nerve damage can also cause absence of position sense where a person is not sure just where his or her feet are and so may be uncoordinated and unsteady when walking. Damage to the autonomic nerves can cause dizziness when standing up, bowel and/or bladder dysfunction, and sexual dysfunction.

How to Minimize or Alleviate Symptoms

If symptoms of peripheral neuropathy develop while taking one of the neurotoxic drugs mentioned, or any other prescribed medication, you should consult your healthcare provider before making any changes in your drug therapy.

Furthermore, people who develop HIV-associated peripheral neuropathy may experience a variety of signs and symptoms at different particular stages

of HIV infection. It is therefore very important to consult your healthcare provider as soon as these symptoms develop so the appropriate treatment can be offered, thus preventing further neurological damage. It is important to note that as the disease progresses, severe pain can be debilitating to some and management of pain medication becomes an important issue. For severe pain caused by peripheral neuropathy, pain medication is most effective when a fixed dose is taken at a fixed time schedule.

Non-medical therapeutic approaches include relaxation training which can reduce anxiety and stress, and subsequently reduce pain and/or promote sleep. Imagery, meditation and visualization techniques can be used for desensitization to anxiety producing stimuli and improve coping with the illness.

Massage therapy can reduce pain and improve sense of well-being. Furthermore, massage therapy promotes arterial and venous blood flow and lymphatic drainage is stimulated, increasing the supply of oxygen and nutrients to sites of pain. Also massage therapy results in passive stretching and elongation of connective and muscular tissue which causes a reduction in muscular tightness and tension. With massage therapy there is systemic release of endorphins and opiates, resulting in pain reduction and a greater sense of well-being.

A diet high in fiber that includes vegetables and fruits, the use of vitamins, especially vitamin B complex, and liberal daily fluid intake are important. Regular daily exercise like walking and stretching exercises to keep muscles flexible should be done as tolerated.

Protective footwear must be worn at all times and should not apply pressure. Shoes and slippers should go over the instep of the foot. Also, it is important to wear warm socks during cold weather. Other safety measures include using a thermometer to test bath temperature; use skid-free shower and bathroom mats; clear walkways of clutter and wipe spills on the floor immediately. Pay close attention to driving skills, particularly the ability to feel gas and brake pedals and changes in your reaction time. If these changes

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The Case Against Zerit *By Bob Huff*

HIV drug therapy works against HIV. This is clear from the dramatic drop in deaths due to AIDS after the use of combination therapy was widely adopted in 1996. But these drugs also act on the body and its metabolism in a number of strange and hard-to-pin-down ways.

In some people, but not all, blood lipids soar to alarming levels that are associated with a higher risk of cardiovascular disease. Yet the rates of heart attack and heart disease in people taking HIV drugs continues to run about the same as those for people without HIV. Antiretroviral therapy may make for some worrisome lab tests, but stopping smoking rather than stopping meds remains a better bet for keeping a healthy heart.

In some people, but not all, fat deposits in the arms, legs and, most visibly, in the face, melt away, leaving people who experience this fat depletion syndrome bearing the tribal scars of facial wasting. When the fat drains from the face, it may be very hard to recover. One option for treating this condition is to undergo an expensive restoration process of soft tissue augmentation using a filler material injected under the skin of the cheeks.

In some people, but not all, the fat that disappears from their faces and thighs seems to end up in their belly as waist sizes bloom. This isn't really what happens, though, and the type of fat that fills the abdomen, called visceral fat, has different qualities from the subcutaneous fat lost from the face and limbs. And not everyone who gains visceral fat loses subcutaneous fat.

And in some people, but not all, insulin tolerance goes out of whack, which may or may not lead to diabetes. (We won't even discuss bone formation problems.)

If you notice a pattern here, it's that what seems to be a definable lipodystrophy syndrome at the 35,000-foot level, becomes a wilderness of associations and anecdotes once you're on the ground. Inconsistent methods, unvalidated measurements and tiny studies make simply defining this complication contentious as researchers continue to tease out the links

between suspected drugs, genetics and HIV itself. So far, no smoking gun has been found and none is expected to turn up. This is, as they say, a multifactorial problem. Scientists looking for answers to this riddle are developing new and more specific lab tests as well as larger and more reliable clinical trials. And clinicians are looking at everything from nuke-sparing regimens to prophylactic glitazones to forestall or minimize the consequences of lipodystrophy. In the meantime, managing the drug-related toxicities of HIV therapy remains an art.

Workers in this ad hoc field recently met in San Diego at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV to trade notes and argue over epidemiology and favorite pathogenesis theories. For those seeking more than a tantalizing intellectual exercise, there was little to write home about.

Zeroing In on Zerit

But the weight may be starting to shift on one lingering dispute. For a long time, whenever talk turned to speculation about which drugs were considered prime suspects for causing lipodystrophy, the name of one culprit always came up: Zerit (d4T or stavudine) is a popular nucleoside analog often combined with ddI or 3TC as part of a three-drug combination. The federal HIV treatment guidelines list d4T among its "strongly recommended" choices for first line therapy. Zerit was linked early on with the nerve damage that causes peripheral neuropathy in some people. Recently it's been indicted for contributing to some of the other unpleasant toxicities of ART, such as facial wasting. Of course, a lot of the charges were stimulated by studies and presentations funded by GlaxoSmithKline, makers of AZT and 3TC, who'd love to see this competitor sent away. And most of the counter-arguments and obfuscation originated with Bristol Myers Squibb, the makers of d4T. So, although many people were resolutely convinced of d4T's guilt, controversy held consensus at bay. This contest may finally be coming to a head as the evidence against d4T solidifies. After data presented this year at the annual Retrovirus Conference, at the International AIDS Conference in Barcelona, and now at the

Lipodystrophy Workshop and the annual ICAAC conference that followed it a few days later, the strength of the associations between d4T and fat wasting are becoming too strong to ignore. As one observer put it, "You can't really say it's just a Glaxo thing anymore."

Mitochondrial Toxicity

The protease inhibitors were the first drug class to take the blame for fat redistribution and lipodystrophy and evidence continues to mount against some of them. But nucleoside analogs have also received scrutiny for their potential to deplete the energy-producing capacity of cells.

The prevailing theory of how nucleoside analogs contribute to fat wasting and elevated lipids revolves around a pathogenic piñata called mitochondrial toxicity. Cellular respiration is the name for a long series of chemical steps in which cells process glucose and oxygen into a useable form of energy. If any of these steps are slowed down or blocked, the whole process backs up and a kind of overflow system starts to consume glucose without oxygen, which dumps a byproduct called lactate into the blood. As an extreme example of what can go wrong with this system, a poison like cyanide can stop cellular respiration dead in its tracks, with rapidly fatal results. But the toxicities thought to be caused by nucleoside analogs are far subtler, so subtle that not all researchers can agree on how, when, where or even if they are happening.

This chain of energy-producing steps takes place mostly within tiny organelles carried inside nearly every cell in the body. These cells-within-cells are called mitochondria, and they possess their own set of DNA instructions to make some of the proteins they need to perform the job of respiration. It's thought that nucleoside analogs, some more than others, can, over time, affect the quantity or quality of several of these crucial proteins by interfering with the replication of mitochondrial DNA. The result can be the generation of excess lactate and an energy deficit in affected tissues; in nerve tissue, neuropathy can be a consequence. Some scientists think a different form of mitochondrial toxicity can trigger a cell to die directly through apoptosis. That could be what's happening to fat cells. Obviously more and better research is needed, fast.

Looking within the Limits

Researchers have been attempting to find a way to directly measure mitochondrial toxicity by quantifying the amount of mitochondrial DNA that can be recovered from cells. Some of this progress was shown at the Lipodystrophy workshop. But serious objections have been lodged against current versions of this technique because they are liable to contamination from other sources of mitochondrial DNA. Next year, the data from mitochondrial toxicity assays may be more convincing, but for now, they're not ready for prime time.

One blood abnormality associated with ART, and with nucleoside analogs in particular, is an increase in blood lactate levels. Slightly elevated lactate levels are not noticeable, but as lactate levels increase, symptoms such as nausea, abdominal pain and distension may become apparent, causing tolerability problems. Lactate levels over 5mmol/L in the presence of symptoms can indicate a rapidly progressing, life-threatening illness called lactic acidosis. All of the nucleoside analogs have been implicated in this rare lactic acidosis syndrome and every person taking them should know the warning signs: nausea, abdominal pain, fatigue or muscle weakness.

But the meaning of moderately elevated lactate levels, called hyperlactatemia, is not certain, although many people believe nucleoside analog-associated damage to mitochondrial DNA is a cause. Older studies of blood lactates are difficult to interpret because of widely varying methods used to collect and analyze the samples. Adoption of a strict new protocol for the standardized collection and processing of blood lactate samples will hopefully help dispel the fog that has surrounded the meaning of these lab values.

One of the first tipoffs that metabolic abnormalities are afoot is when blood lipid levels start to climb. The key movers are total cholesterol and triglycerides. Rising cholesterol raises eyebrows because of its association with cardiovascular disease — cholesterol can clog the arteries feeding the heart and set off a heart attack. But the underlying metabolic problems causing the cholesterol rise and the role ART

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plays are still mysteries. The same is true of the rise in triglyceride levels experienced by some people on ART. Sustained high triglycerides may be a predictor for developing pancreatitis or diabetes, and increasing rates of diabetes in people on ART is a growing problem. How and why this is happening isn't certain. Still, most clinicians would feel more comfortable if their patients could achieve decent viral suppression without the abnormal labs.

A number of studies looking at lipid abnormalities have pointed the finger at protease inhibitors and at ritonavir in particular as causative factors. Recently a few more studies have shown that nucleoside analogs add their own bump to cholesterol and triglycerides. And a few high quality studies are starting to examine the associations with actual fat loss and recovery.

Andrew Hill told the Lipodystrophy Workshop that there is a "Tower of Babel" when it comes to reporting drug toxicities in clinical trials, with at least seven different ways of reporting abnormal lab values. Graded levels of toxicity are far less sensitive than using continuous values such as changes in area-under-the-curve. Drug company trials can either hide or accentuate toxicities depending on the method chosen to report events. Often these studies just add to the noise.

Leaping Lipids

Until recently, most of the research pointing the finger at Zerit used methods that were easy to dismiss, such as small sample sizes, no controls, and uneven reporting criteria. But this latest wave of evidence is not so easily ignored.

A study presented in Barcelona (Gilead 903, sponsored by Gilead Sciences, Inc., the makers of tenofovir) compared d4T with tenofovir in 600 people over 48 weeks. All volunteers received efavirenz and 3TC. It was their first experience with HIV treatment. By the end of the nearly year-long study, viral load reductions were about the same in both groups. But there was a striking difference in the cholesterol and triglyceride levels between those who took tenofovir and those who took d4T. Triglycerides were unchanged from baseline in the tenofovir

group but went up by 74mg/dl in the d4T group. Cholesterol also went up by 24mg/dl in the tenofovir group but increased by twice that amount in the d4T group.

More data from Gilead 903 on the lipid profile of tenofovir versus d4T was presented at ICAAC by Joel Gallant of Johns Hopkins University. This trial is scheduled to run for three years, which counts as long-term compared to most studies, but is little more than a honeymoon in terms of how long most people will be taking these drugs. So far, one year in, only lab toxicities have been observed. Gallant made a point of stressing the need for longer-term studies to help accumulate data that might finally correlate lab values with clinical outcomes.

Earlier in the year, a Glaxo-funded study (ESS 40002) showed similar findings at the Retrovirus Conference. As a part of this trial, 111 treatment-naïve patients received nelfinavir plus 3TC and either AZT or d4T as the third drug in their regimens. With nelfinavir in the mix, some increases in cholesterol and triglycerides would be expected. But while people receiving AZT had cholesterol increases averaging 32mg/dl, those on d4T had average increases of 45mg/dl. For triglycerides, the results were even more striking with the AZT group seeing a bump of 31mg/dl while the d4T group saw an average increase of 69mg/dl, over twice as much.

Lactates in the Dock

In addition to looking at cholesterol and triglycerides, the Glaxo-funded ESS 40002 study also recorded lactate levels at baseline and after 48 weeks. While people taking AZT experienced an average lactate increase of 2.3mmol/L, those on d4T had increases over three times higher, at 7.9mmol/L, well into the danger region.

Another Glaxo-funded study presented at ICAAC (TARHEEL) looked at what happened when treatment-experienced patients who had been on a regimen containing d4T and were experiencing lipodystrophy switched to either AZT or abacavir. A set of 16 people with elevated lactates stopped all treatment until blood values showed a return to safer levels. Treatment was then restarted without d4T. At 48 weeks, lactate levels remained controlled within a normal range. Although this small substudy lacks a control arm for

comparison, the results give guidance to a clinician seeking to normalize hyperlactatemia in a patient.

The Proof is in the Padding

Laboratory abnormalities are intriguing for scientists and alarming for clinicians but they are likely to be bewildering to people on HIV treatment. It's often the changes in the way they look in the mirror that matters foremost. Several studies are now starting to connect the dots by evaluating changes in fat deposits under the skin over time. For fat losses in the arms and legs, a technique called DEXA is reliable and well accepted. For increases in fat around the organs, a CT scan is a more acceptable, and more expensive, method. For fat loss in the face, patient self-evaluation or photography of facial fat wasting tell the story, but these, unfortunately, do not carry the same weight as more objective readings such as DEXA.

The report that's gotten everyone's attention comes from a large trial that compared nelfinavir to efavirenz at the same time it compared AZT/3TC with d4T/ddl in people starting their first ART regimen. The trial, called ACTG 384, was conducted by the federally funded AIDS Clinical Trials Group. Results were first presented in July, 2002 in Barcelona and an additional analysis of fat loss was presented at the Lipodystrophy Workshop.

The fat loss substudy of ACTG 384, (ACTG 5005s) measured subcutaneous fat by DEXA in the arms and legs of 157 volunteers at baseline. The results from comparisons at weeks 48, 64 and 80 were presented. Overall, people in both the AZT/3TC group and the d4T/ddl group experienced a brief increase in subcutaneous fat during the first weeks after starting treatment. This may be due to a general improvement in constitutional health that follows the initial suppression of viral load. But by week 48, the average amount of subcutaneous fat in the arms and legs had declined by 7.5% in those on d4T/ddl, and was starting to drop, but still above baseline, in those on AZT/3TC. By week 80, the d4T/ddl group was down about 15% on average, while the AZT/3TC had slipped by about 7%.

When the same group was analyzed by whether they were on nelfinavir or efavirenz, not surprisingly, a greater loss of limb fat was associated with being on the protease inhibitor. At week 80, those on nelfinavir plus nukes were down by 18%, while

those on efavirenz had sustained a 10% fat loss on average. A breakout of results by individual three-drug combinations was not shown and the role of d4T relative to ddl in causing fat wasting cannot be determined from this data.

The TARHEEL study that looked at lactates also measured changes in subcutaneous fat by DEXA after the switch was made from d4T. Of the 118 people with lipodystrophy who enrolled, over 80% had been on d4T for over two years. Three-quarters of the volunteers switched to abacavir and the rest to AZT. At 48 weeks, the biggest improvement was noted in the arms, with those on abacavir experiencing an average 37% increase in subcutaneous fat and those on AZT a 17 percent gain. Fat gains to the legs were less profound, with abacavir associated with a 15% average increase and AZT with about half that. However, a comparison of CT scans of visceral fat at baseline and at 48 weeks did not show a significant change. As with the lactate data, this is a before-and-after study with no concurrent control, and other factors may have played a role in these effects. Yet with the weight of evidence now implicating d4T in accelerated subcutaneous fat loss, when is reasonable doubt overruled by unreasonable risk?

Do You Feel Lucky?

It's likely that all of the nucleoside analogs contribute to mitochondrial toxicity, some in some cells more than others; some sooner than others. But d4T seems to offer a fast track to fat wasting for far too many people who start taking it. Of course, not everyone is affected, that's the quandary. Some people still have fat and happy cheeks after years on d4T. If their viral load is suppressed and they tolerate their drugs they'll probably see no reason to switch. But people choosing a regimen today have a different decision to face, and there's no way to predict how things will go. If Zerit accelerates fat wasting, then there may be better first choices for a nucleoside analog.

Many people on treatment and their doctors pronounced Zerit guilty long ago. The next hearing should come when the committee that writes the federal treatment guidelines meets again to redraw their recommendations.

HIV News

Heart Disease from HAART?

by Mark Katz, MD

A randomized trial of 1551 Italian patients compared the use of NNRTIs to PIs in their association with cardiovascular complications (Barbaro G et al., #WeOrB1307). An interesting and frequently quoted data piece from this study is that 87% of the subjects were smokers - and that a smoker was defined as someone who smoked *more than a pack per day!*

Subjects were evaluated every four months over a three-year period, and there was a statistically significant increase in coronary events (angina pectoris, as well as myocardial infarction) in persons who had the PI therapy as compared to NNRTIs. In addition, the presence of lipodystrophy was correlated with greater risk of cardiovascular disease.

In another related study (Holmberg S et al., #TuPeB4494), the chance of having a heart attack was likewise increased while taking a PI.

Many conference experts and reviewers concluded that on the basis of these cardiovascular studies, along with the superiority of the NNRTI arm in ACTG 384, that the use of PI-sparing regimens will increase in the months to come.

(Remember: The major question not as of yet definitively answered is: If there is an association between certain antiviral drugs and heart disease, is it due to the lipid elevations - which these drugs are known to cause, and which are clear risk factors for the development of heart disease? Or, are there other factors (in addition or instead) which may make someone living with HIV, with or without medication, more likely to develop cardiac problems? And in any case, these studies should not be construed as an invitation to stop HAART, or PI, therapy, especially if it is working well. But it does invite more to be learned... and soon...)

A review of the efficacy of HAART in preventing the serious opportunistic complications which used to cause tremendous loss of life in persons with AIDS was presented from the Denver cohort (Cohn et al., 1443). The rates of both disseminated MAC as well as CMV infection decreased 89% and 88% respectively in the period from 1990 to 2001.

(This information underscores the notion that while we are delving into potential downsides of HAART therapy, that we should not forget the changes which befell the epidemic in the late 1990s as a result of

their use.)

Results from the FRAM (Fat Redistribution and Metabolic Changes) study were presented by Carl Grunfeld (#158) et al.. This is a cross-sectional look at a random sample of HIV+ men (>800) as well as women (>350), both on and off therapy - compared to a non-HIV database matched for age and gender. The study findings affirm that while fat loss clearly occurs more commonly in HIV+, that waistline fat gains (formerly called by such names as "protease paunch") are actually comparable in the HIV-negative cohort as in those infected.

(Remember: These results do not exclude the reality of fat gain as an issue for some persons living with HIV - but once again underscore how scientific validation via statistical analysis and watchful observation and/or experiments sometimes adds a slightly different "spin" to an issue than originally envisioned.)

Regarding another known potential complication of HIV/AIDS, the wasting syndrome, a variety of treatments have been proposed over the years. The one FDA-approved remedy for this is human growth hormone (Serostim) - and this year's Conference included multiple studies on its potential usefulness as a remedy for lipodystrophic changes.

One of these, presented by Donald Kotler, MD (#LbOr18), was a placebo-controlled multicenter trial in 239 patients, measuring changes in visceral adipose tissue (VAT) as well as serum cholesterol (non-HDL). The treatment lasted for 12 weeks, and those receiving growth hormone got either daily or every other day doses of 4 mg subcutaneously. There was a significant improvement in the fat measurements back towards normal in the group with daily injections, and nearly statistically significant in the group receiving it every other day.

The ultimate role for Serostim as a treatment remains to be elucidated, but this study certainly is on the road towards validating its potential.

Interrupting HAART

by Mark Katz, MD

Mark Dybul and group (#261) presented some updated information on patients receiving structured intermittent treatment. In one cohort of 10 patients, who had been maintained on a combination of d4T + 3TC + ritonavir/indinavir, they were then switched to alternating one

week on therapy with one week off. In a year of follow-up, there was no significant rebound (although some "blips" occurred) and a trend towards lower lipid levels.

Another eight patients were alternating weekly ddI + 3TC + efavirenz with a week off therapy, and at week 24 there was no rebound and no blips.

In a larger observational database of 101 patients who stopped therapy (Parish MA et al., #1439), 67% remained off therapy at a mean of 74 weeks, with an average last CD4 of 508. (Patients were asked to resume antiviral therapy if the viral load went back up and/or CD4 count declined beyond certain parameters.)

There were no opportunistic infections or malignancies, although two patients developed acute retroviral syndrome (presumably from resumption of viremia) and two developed a low platelet count (thrombocytopenia) - a symptom sometimes seen in untreated patients.

As one might expect - but now the numbers are there with statistical validation and significance - the greater the pre-interruption CD4 was, the longer the patient is likely to remain off therapy. Also, those whose numbers were such that they would have met DHHS guidelines for treatment were 2.9 times as likely to have to resume medication.

(This information affirms what many clinicians and patients have been doing: If viral load is well suppressed and CD4 count is high, stopping treatment with ongoing observation. As most have intuited or anecdotally observed, the better the number were originally and/or at the time of interruption, the greater the chance of staying off therapy longer. Most experts would not recommend this for anyone with advanced HIV infection, or AIDS.)

Being Alive, August/September 2002

Pharmacor Receives U.S. Patent for Anti-HIV Integrase Inhibitor

Pharmacor Inc. has been issued U.S. patent application no. 09/963,329 relating to its antiretroviral program. The small-molecule compounds described in the patent, entitled "Aromatic derivatives with HIV integrase inhibitory properties," are novel anti-HIV lead molecules that target a novel mechanism of action on the human immunodeficiency virus.

"The integrase enzyme is a very complex protein that HIV uses to incorporate its genetic material into the human DNA," states Dr. Jocelyn Yelle, VP. Of R&D. "Because of its complexity, scientists have had a hard

time finding drugs that can inhibit its function. Pharmacor's new integrase inhibitors carry the necessary pharmacophores needed to block the viral enzyme."

"Our ability to target the integrase enzyme places us among a very elite group of drug discovery companies," notes Dr. Brigitte Lebreton, President and CEO of Pharmacor. "Developing an anti-integrase drug will add a third target to the anti-HIV drug arsenal. Expanding the options available to HIV-positive patients increases the possibilities for a successful drug cocktail (HAART)."

The HIV replication cycle involves a sequence of three enzymes: transcriptase, protease, and integrase. Currently there are 16 AIDS drugs on the market, ten target the reverse transcriptase enzyme and six target the protease enzyme. The advent of drug-resistant strains of the virus has created the need for new drugs that demonstrate unique resistance profiles or target novel mechanisms of action. There are no anti-integrase drugs on the market today.

Pharmacor has spent four years developing its compound library of small-molecules targeting HIV viral integrase. Three independent families of compounds are currently under investigation. The hydroxyphenyl derivatives, aromatic derivatives, and one other family of compounds with patent pending. The Company now holds a total of five patents issued by the USPTO, two patents cover two anti-integrase families of compounds and three patents cover three anti-protease families of compounds. *PRNewswire, December 18, 2002*

"Viral Jujitsu"

"Viral Jujitsu" is the title of an article one of our technical reviewers thought was of interest. It was a one page article in FORBES (magazine), March 3, 2003, page 117, by Mary Ellen Egan. She points out that antiretroviral drugs slow, but do not eliminate HIV. A new gene therapy produced by the small biotech firm Virxsys of Gaithersburg, MD embeds a "...lentiviral vector in the body's own disease-fighting T cells" and that "...may come a little closer toward actually curing AIDS."

The lentiviral vector's RNA binds with the HIV to "activate proteins that chew up the virus' reproductive genes as soon as it begins to replicate." T cells, grown outside of the body with the lentiviral vector inside them, would be injected into the HIV patient. The article quotes Virxsys founder and chief scientist, Boro Dropulic, "...it may be possible to cure patients with AIDS by creating an army of T cells that can inhibit and

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resist HIV infection." He also explained that current drugs have up to a dozen binding sites and the HIV is able to mutate in such a way as to reduce their effectiveness. The lentiviral vector that Virxsys is working with, however, has 937 sites that would require the HIV to mutate hundreds of times to become resistant. He points out, "And the more it mutates the weaker it gets." Early reports show that the lentiviral inhibited HIV replication by 99.9% in T cells.

As a cautionary note the article points out that other gene therapy studies have had significant problems with

limited human trials. The article states that Dropulic has been testing the lentiviral vector's safety using human tissue in mice and the Food and Drug Administration gave him permission "in December to enroll a handful of patients for early-stage clinical trials at the University of Pennsylvania."

HIV Develops Resistance to Experimental Drug

The experimental AIDS drug T-20, which researchers hope will benefit people whose HIV infections have become resistant to other medications, may itself sometimes cause HIV resistance to develop, suggests a new study in *Antimicrobial Agents and Chemotherapy* (2002;46:1896-1905). The resistance developed in a study of patients taking T-20 alone, not in combination with other medications. Recently, Roche Holding AG, which is developing the drug with Trimeris Inc., reported encouraging results of studies of T-20 used in combination with other AIDS drugs.

"Both studies indicate that T-20 significantly enhances the activity of HIV combination therapy," said Dr. Dani Bolognesi, CEO and chief scientific officer of Trimeris. The cases of HIV resistance developed in an early-phase trial designed to test the safety of the drug in humans, he said. That resistance was only in patients taking a lower dose than is being tested in later trials of T-20, which are ongoing. Resistant viruses have not developed in those studies, according to Bolognesi.

Unlike current AIDS drugs that target HIV once it has already entered cells, the fusion inhibitor T-20 works by keeping HIV from entering cells in the first place.

In the study, Dr. John C. Kappes and colleagues at the University of Alabama-Birmingham studied 16 HIV-positive patients. Patients took 3 mg, 10 mg, 30 mg or 100 mg of T-20 twice a day for two weeks. In

patients taking the two lowest doses, there was no noticeable effect on the viral load. In all patients taking the highest dose, however, viral load dropped below detectable levels. Resistance developed in patients taking the 30 mg dose. These patients experienced

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Overcoming Peripheral Neuropathy (cont.)

occur, refrain from driving immediately and discuss this with your healthcare provider.

Finally, HIV-infected people with symptomatic peripheral neuropathy should consider participation in one of the many clinical trials of treatments for the associated discomfort from this disease. Your healthcare provider can assist you with enrollment in clinical trials.

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Management of Hepatitis C

A Review of the NIH Consensus Development Conference

By Kelly A. Gebo, MD, MPH and John G Bartlett, MD

The National Institutes of Health (NIH) convened a Consensus Development Conference June 10-12, 2002. The primary sponsors of the meeting were the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Office of Medical Applications of Research (OMAR) of the NIH. The event was co-sponsored by several different agencies within the Federal Government that have an interest in hepatitis C, particularly the National Institute of Child Health and Human Development (NICHD); the National Cancer Institute (NCI); the National Center for Complementary and Alternative Medicine (NCCAM); the National Institute on Alcohol Abuse and Alcoholism (NIAAA); the National Institute on Drug Abuse (NIDA); the National Institute of Allergy and Infectious Diseases (NIAID); the National Heart, Lung, and Blood Institute (NHLBI); the Centers for Medicare & Medicaid Services (CMS); the Centers for Disease Control and Prevention (CDC); the U.S. Food and Drug Administration (FDA); and the U.S. Department of Veteran Affairs (VA). The Agency for Healthcare Research and Quality (AHRQ) provided support to the Conference through its Evidence Based Practice Center Program. Under contract to AHRQ, the Johns Hopkins University Evidence Based Practice Center developed a systematic review of the literature and analysis that served as a reference for discussion at the conference and is available at

<http://www.ahrq.gov/clinic/epcsums/hepcsum.htm>.

This 2-1/2 day conference examined the current state of the art regarding management for hepatitis C and identified directions for future research. During the first day and a half, experts presented the latest hepatitis C research findings to an independent non-federal panel. After weighing all of the scientific evidence, the panel drafted a statement, which addressed the following questions:

1. What is that natural history of hepatitis C?
2. What is the most appropriate approach to diagnosing and monitoring infected patients?
3. What is the most effective therapy for hepatitis C?
4. Which patients with hepatitis C should be

treated?

5. What recommendations can be made to patients to prevent transmission of hepatitis C?
6. What are the most important areas for future research?

On the final day of the conference, Dr. James Boyer, the panel chair, read the draft statement and invited the audience to comment. A press conference followed to allow the panel and chair to respond to questions from the media. The draft statement was posted on the consensus website <http://consensus.nih.gov> on Wed. 6/12/2002, a final draft will be posted on or about 9/9/2002.

Natural History of Hepatitis C

Hepatitis C is an RNA virus of the flaviviridae family. There are 6 HCV genotypes and more than 50 subtypes. The genotypes can differ by as much as 30% to 50% in their nucleotide sequences. The virus also has a high propensity to mutate. The lack of a vigorous T cell response appears to promote a high rate of chronic infection. Genotype 1 accounts for 70%-75% in the U.S. and has a poorer response to treatment. During acute infection the viral load can range from 10^5 to 10^7 [IU/mL]. Chronic HCV levels are variable and can range from 50,000-5,000,000 IU/mL; within the same person, they are generally stable.

According to the National Health and Nutrition Examination Study (NHANES), conducted by the Center for Health Statistics (NCHS) at the CDC, it is estimated that there are over 2.7 million people in the U.S. living with chronic HCV infection. This may be an under-estimate, however, since the NHANES household survey did not include high prevalence populations such as incarcerated, homeless, or institutionalized persons. There are an estimated 35,000 new infections per year, and the prevalence in the U.S. is 1.8%. The highest prevalence is seen among adults aged 40 to 59 years and among African Americans, who have a prevalence of 6.1%. Seroprevalence among inmates, the home-less, and hemophiliacs is 15%

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to 50%; among IDUs, it is 70% to 90%.

After initial exposure, HCV RNA can be detected in the blood at 1 to 3 weeks. Antibodies to HCV are detected by enzyme immunoassay (EIA) in approximately 50% to 80% of patients at the onset of symptoms, and this increases to 90% at three months. ALT levels are elevated at 2 to 8 weeks. Acute infection can be severe but is rarely fulminant.

Chronic HCV is defined by the detection of HCV RNA for at least 6 months. In general, prospective studies have suggested that approximately 80% of HCV infected patients develop chronic infection. Factors associated with spontaneous clearance of the infection include younger age, female gender, and certain histocompatibility complexes. African-Americans appear to be least likely to spontaneously clear the infection.

The major late sequelae of chronic infection is cirrhosis, which is seen in 20% to 25% after 20 years (in retrospective studies) and in 2% to 4% (in prospective studies). This risk is not influenced by viral load, viral genotype, or quasi species diversity. However, host risks for cirrhosis include longer duration of infection, older age, male gender, immunosuppression (HIV infection), HBV co-infection and alcohol use (defined as 40-60 g/day). Other factors include iron overload, nonalcoholic fatty liver disease, and hepatotoxic medications. One-third of patients with hepatocellular cancer (HCC) have HCV as a risk factor. HCC rarely occurs without cirrhosis or advanced fibrosis. The incidence of HCC is continuing to rise in the U.S. and worldwide. Extra hepatic manifestations of HCV include rheumatoid symptoms, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia and are thought to be of immunologic origin. Cryoglobulins have been found in up to one-half of patients with chronic HCV infection, but symptoms occur significantly less frequently.

What is the Most Appropriate Approach to Diagnosis and Monitoring?

EIA tests are reproducible, inexpensive, and are

approved by the FDA for the diagnosis of HCV. They are suitable for screening at risk populations, as they have a very high sensitivity and specificity (exceeding 99%). A negative EIA excludes the diagnosis in immunocompetent patients, but not in immunodeficient patients. False positives occur with autoimmune disorders, and these cases require HCV RNA for confirmation with RIBA.

Persistent HCV infection in a patient with a positive EIA should be confirmed with a PCR. The FDA-approved qualitative HCV PCR has a threshold detection of 50 IU/mL. Transcription-mediated amplification (TMA) has a lower threshold for detection, but is not approved by the FDA. Sensitivity of these assays is over 98%. Testing for HCV RNA can provide an accurate assessment of the HCV viral titer. Viral load (HCV RNA level) is measured by quantitative PCR (qPCR) or branched DNA (bDNA) and reported in international units (IU). Significant variability exists between available assays. While there is little correlation between disease severity or progression with the absolute titer of HCV RNA, determination of the quantitative HCV titer can provide important information in assessing the response to treatment.

Serum alanine aminotransferase (ALT) is the least expensive test to measure disease activity, but it does not correlate with severity of histopathology by liver biopsy. Serial measurements are recommended for monitoring, but do not assess progression to cirrhosis.

Liver biopsy provides information on fibrosis and histology assessment and information about concurrent liver disease due to other causes. It may help guide the decision regarding therapy: Absent or minimal fibrosis may encourage deferral, though the response with genotypes 2 or 3 is so good (80%) that routine pretreatment biopsy is sometimes considered unnecessary.

Hepatocellular cancer screening is not well studied in HCV patients. While the incidence of HCC is 0% to 3% per year after the onset of cirrhosis, no study has been able to identify a screening or surveillance protocol that improved long-term survival. One study evaluating alpha-fetoprotein and ultrasound every six months in

patients with HCV showed earlier detection of HCC, but no survival analysis was performed. Therefore, further studies are needed to identify the most appropriate HCC screening protocols.

What is the Most Effective Therapy for Hepatitis C?

Since the 1997 NIH Consensus Development Conference on Management of Hepatitis C, many new therapies have been identified. Combination therapy results in better treatment responses than monotherapy. The highest response rates have been found with pegylated (PEG) interferon in combination with ribavirin. Genotype determinations influence treatment decisions as genotypes 2 and 3 have much higher response rates than genotypes 1 and 4.

The best indicator of effective therapy is “sustained virological response” (SVR), defined as the absence of qualitative HCV RNA by RT-PCR after 24 weeks of treatment. The highest response rates have been demonstrated in the trials with PEG-interferon plus ribavirin. Of note, these trials excluded patients with decompensated liver disease, cirrhosis, and other medical comorbidities.

<p>• Initial SVR results are similar</p>		SVR	<p>Treatment: results are for PEG-interferon</p>
	Genotype 1	42-51%	
	Genotype 2-3	76-82%	

alpha 2A or alpha 2B when each is combined with ribavirin. Results of three large pivotal studies are summarized below:

In all three trials, the SVR for genotype 1 was based on higher doses of PEG-IFN and ribavirin for 48 weeks.

Treatment for 24 weeks with lower dose ribavirin appears adequate for genotypes 2 and 3. Early viral response (EVR) is defined as a two-log decrease in viral load. EVR at 12 to 24 weeks of treatment predicts SVR, and those who fail to achieve EVR have little probability of achieving SVR even if therapy is continued a full year. Of note, SVR has not yet been correlated with improved survival. However, longer-term follow-up of these patients is currently in progress.

• **Re-treatment:** Decisions regarding re-treatment should be based on the following:

1. Previous type of response.
2. Previous therapy and the difference in potency of new therapies.
3. Severity of underlying liver disease.
4. Viral genotype and factors predictive of response.
5. Tolerance of and adherence to prior therapies.

Definition of Previous Treatment Response

Relapsers are defined as patients who achieved an “end of treatment response” (ETR) that is not sustained over time. In these patients, re-treatment with standard interferon using the same regimen is generally unsuccessful. The use of PEG-interferon plus ribavirin in a patient previously treated with interferon mono-therapy has not been evaluated. When a new regimen of the standard drugs (such as higher dose or longer duration of standard interferon plus ribavirin) is used in a patient previously treated with interferon alone, re-treatment is more effective in those who have relapsed compared with those who failed to respond.

Non-responders are defined as those who fail to achieve EVR, ETR or SVR. Preliminary data suggest that 15% to 20% of these patients who have received treatment with standard interferon and ribavirin will achieve SVR with re-treatment with PEG-IFN and ribavirin. Patients with genotypes 2 or 3 have better response rates to re-treatment than those with genotype 1.

Partial responders are a subset of non-responders who have a viral load reduction of 1-2 logs₁₀ c/mL during treatment. Re-treatment of these patients may be associated with improved histology despite absence of SVR.

Other factors in the decision for re-treatment include the severity of liver disease, since those with advanced fibrosis or cirrhosis should be considered a higher priority for re-treatment. The possible role of maintenance therapy using PEG-interferon monotherapy in patients with advanced fibrosis or cirrhosis is currently being studied in the HALT-C trial; however, this strategy is considered experimental until these

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results are available.

Side effects are severe enough to require discontinuation in 20% of patients in the PEG-interferon and ribavirin registration trials. The most common side effects are influenza-like symptoms, bone marrow suppression, and neuropsychiatric symptoms. Often these side effects can be adequately treated with growth factors and antidepressants.

Indications For Treatment

All patients with chronic hepatitis C are potential candidates for antiviral therapy. The major indication for treatment is the risk for progression to cirrhosis based on measurable HCV RNA and liver biopsy showing portal or bridging fibrosis and at least moderate inflammation and necrosis. Age and prior behavior should not be factors in the decision to treat. Modifying circumstances include:

- **Normal ALT:** Thirty percent of patients with chronic HCV have a normal ALT, and an additional 40% have elevated levels that are less than two times the upper limit of normal (ULN). Currently, "experts differ on the indications for biopsy and treatment" and studies are underway to identify patients most likely to benefit from treatment. Notably, studies of PEG-interferon and ribavirin have not been completed in patients with normal ALT levels.
- **Biopsy results:** In patients with elevated ALT and no fibrosis plus minimal inflammation, the current recommendation is to monitor liver function tests and potentially to repeat the liver biopsy in 3 to 5 years. In patients with advanced liver disease (advanced fibrosis or compensated cirrhosis), sub-group analysis of studies to date have shown lower rates of SVR. However, this group of patients is being evaluated in the HALT-C trial, which should provide recommendations on re-treatment. In patients with decompensated cirrhosis, the main treatment is transplantation. Although re-treatment should be considered, this approach may be limited by potentially life-threatening side effects of antiviral therapy.
- **Acute HCV:** Currently the data available are inadequate for making a recommendation.
- **Injection drug users:** Data are available for treatment of HCV-infected IDUs who are in drug treatment programs. These studies show

success even with continued drug use or with concurrent methadone treatment. Therefore, efforts should be made to promote collaboration between HCV experts and substance abuse providers. It should be noted that there are few data available on HCV treatment in active IDUs who are not in drug treatment programs.

- **HIV coinfection:** All HIV infected patients should be screened for HCV. Coinfection accelerates the course of HCV and HIV. Although there are no HCV therapies specifically approved for patients with HIV, these patients should be considered for treatment. Thus far, studies have only enrolled patients with stable HIV infection and well compensated liver diseases. However, in these patients, SVR can be achieved, and preliminary data suggest better responses to PEG-interferon with ribavirin than to standard interferon and ribavirin. Although treatment of HCV has not jeopardized control of HIV infection, additional studies are needed to further evaluate this possibility.

- **Alcohol:** Continued use of alcohol adversely affects outcome of treatment. Currently, treatment of HCV should be performed in conjunction with efforts to treat alcohol dependence. Heavy alcohol use (>80 g/day) seriously compromises HCV treatment; therefore, HCV treatment should be combined with abstinence whenever possible.

Reduction In Transmission

Injection drug use accounts for over two-thirds of new infections; therefore, it is assumed that drug rehabilitation and needle exchange programs should reduce transmission. Sexual transmission appears to be infrequent based on a seroprevalence of only 2% to 3% in partners of HCV-infected persons in long-term monogamous relationships and 4% to 6% among persons with multiple sex partners, sex workers and those at risk for sexually transmitted diseases. For heterosexual discordant couples, the estimated risk of transmission in this setting is 0% to 0.6% per year, with the risk to females being three-fold greater than to male partners. Use of condoms may decrease HCV transmission and should be encouraged, especially for those at risk for other sexually transmitted diseases. The risk of occupational exposure with a needle stick injury from an HCV-infected source is about 2% and currently postexposure antiviral therapy is not

recommended. Perinatal transmission is approximately 2% for infants from an HIV infected mother and is higher with high maternal viral load, injection drug use (10%), and with HIV co-infection (20%). Ribavirin and interferon are contraindicated during pregnancy and there are no data on Caesarean section and the risk of transmission. Breastfeeding does not appear to transmit HCV. Low transmission rates (less than 1%) are associated with body piercing and tattooing.

Conclusions

The panel recommended that the NIH establish a Hepatitis Clinical Research Network. The goal of this network should be to conduct research related

to the natural history, prevention, and treatment of hepatitis C. In addition, they recommended organizing randomized controlled trials to extend treatment to special populations not represented in current trials to determine the applicability of current antiviral combinations in those with acute hepatitis, hemophilia, stabilized depression, and HIV co-infection, as well as in IDUs and alcoholics. Such an effort should lead to decreased HCV related morbidity and mortality as well as a decrease in the reservoir of disease.

Comment from authors: This summary is based on the draft guidelines. There may be changes to the final version, but we expect that they will

Hepatitis Weekly, February 10, 2003

Hepatitis C/HIV Coinfection: Prolonged HAART May Cause Higher HCV

Load in HIV Coinfected

BYLINE: Sonia Nichols, senior medical writer

Long-term use of highly active antiretroviral therapy (HAART) may be responsible for raising hepatitis C virus (HCV) loads in patients coinfecting with human immunodeficiency virus (HIV).

Researchers at Stanford University School of Medicine in California have detected higher HCV viral loads and greater quasispecies diversity in such individuals, according to a report in the February 2003 edition of *Journal of Virology*.

"Three cohorts of coinfecting patients were analyzed retrospectively over a period of 7 to 10 months: group A was antiretroviral drug naïve at baseline and then on HAART for the remainder of the study, group B did not receive antiretroviral therapy at any point, and group C was on HAART for the entire study," said Jennifer M. Babnik and colleagues. Researchers sequenced the hyper variable region 1 of HCV in order to detect quasispecies formation.

"In a longitudinal analysis, there was no significant change from baseline in any immunologic, virologic, or quasispecies parameter in any of the three groups," Babnik and coauthors noted.

Even so, individuals in group C developed significantly higher CD4+ and CD8+ cell counts than those in the other groups did. Those patients also had higher viral loads than those in the other groups. Finally, there was greater quasispecies diversity among patients in group C.

People infected with HCV genotypes 2 or 3 showed stronger immune response and gene activity than others infected with HCV genotype 1 (Impact of highly active antiretroviral therapy and immunologic status on hepatitis C virus quasispecies diversity in human immunodeficiency virus/hepatitis C virus-coinfecting patients. *J Virol*, February 2003;77(3):1940-1950).

"These results suggest that there is no immediate effect of HAART on HCV but that, with prolonged HAART, immune restoration results in an increase in HCV load and quasispecies diversity," researchers concluded.

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Key points reported in this study include:

- * Patients coinfecting with HCV and HIV who take HAART for a long term are subject to experiencing immune restoration.
- * Immune restoration may lead to increased HCV viral loads in HCV/HIV coinfecting patients.
- * Long-term HAART use may also lead to greater HCV quasispecies diversity in HCV/HIV coinfecting patients.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

What Did We Learn About Hepatitis C From AASLD

2002? Part 1 *by Alan Franciscus, Editor-in-Chief*

The 53rd annual meeting of the American Association for the Study of Liver Diseases was held in Boston Massachusetts from November 1st thru November 5th. In attendance were over 4000 hepatologists and hepatology health professionals from all around the world to exchange the latest liver disease research, discuss treatment outcomes and interact with their colleagues. This is known to be the premier meeting in the science and practice of hepatology where the cutting edge in the study and treatment of liver and biliary disease is defined.

In Part I, we are going to recap the highlights of the conference as they relate to the natural history of hepatitis C. In this article you will learn some new information regarding the rate of disease progression and whether it is the same throughout life, the effect of fat in the liver (steatosis) as well as the effect that alcohol has on the rates of viral eradication. This article will close with some very interesting data on the treatment of hepatitis C in patients awaiting liver transplantation, which is going to become more and more important as patients are diagnosed with advanced liver disease and as hepatitis C awareness increases. In Part II (next month) you will learn what is new from a treatment standpoint which will include both promising treatments on the horizon as well as those currently or soon to be available.

Firstly, from a Twin Biopsy Study in the United Kingdom (abstract #607), researchers looked at risk factors for the progression of fibrosis. The study found that the following were risk factors: fibrosis score on first biopsy, age at first biopsy, necroinflammatory score, iron on biopsy and mean duration of infection with the first two factors being the most important determinants of fibrosis progression. The researchers also determined which factors were NOT predictive of progression of fibrosis and these included: HCV genotype, route of transmission, gender (M/F), alcohol intake (less than 6/week in the majority of patients), ALT levels (both mean and peak), steatosis on biopsy or prior HBV infection. The researchers of this study concluded that fibrosis

is not linear (does not progress at the same rate throughout life) which suggests that patients with higher levels of fibrosis maybe be at a higher risk of fibrosis progression than those with no or low levels of fibrosis. This study has important clinical implications as the current recommendation is to perform a liver biopsy every 4-5 years in untreated patients. Based upon these findings this may need to be modified so that patients with more fibrosis may need to get a biopsy every 2-3 years. Age is also important in that older patients with fibrosis are more likely to be at the higher risk of fibrosis progression. On the other side are patients with no or minimal fibrosis who, based upon this data, probably need a liver biopsy even less often than every 4-5 years.

Secondly, as it relates to hepatitis C and steatosis (fat in the liver), there were some new findings at the AASLD conference. It was concluded by the researchers (abstract # 408) that the following factors are associated with steatosis: fibrosis score and presence of cirrhosis (but not inflammation), BMI (Body Mass Index) average 26.5 for grade 0 and 29.2 for grade 3, HCV RNA levels and HCV genotype 3. It was interesting to note that in this study in a multivariate analysis, alcohol use, cholesterol, triglycerides, and glucose were not associated with steatosis. The fact that HCV genotype and viral load are related to the presence of steatosis suggests that the virus plays a unique role in fat turnover and transport within liver cells. In addition, the fact that steatosis is associated with fibrosis but not inflammation suggests that liver fibrosis occurs by a unique mechanism which is non-inflammatory. In addition to the above mentioned findings, the researchers concluded that achieving an optimum weight may be important in reducing the risk of fibrosis in patients with hepatitis C. Another abstract focusing on steatosis (abstract 416) looked at the difference in steatosis between patients infected with different genotypes (genotype 1 and 3) and further clarified the metabolic association in steatosis. This study provided strong evidence that genotype 3 virus but NOT genotype 1 virus is

important in modifying hepatocyte lipid turnover and transport. This information suggests that there are two different mechanisms for fatty liver in patients with hepatitis C infection. In HCV genotype 3 there is a direct effect of the virus on steatosis and, therefore, eradicating the virus would have a significant impact on the steatosis. On the contrary, steatosis associated with other genotypes is related to metabolic abnormalities including obesity, hyperlipidemia and diabetes. In the non-genotype 3 patients, steatosis needs to be managed through the metabolic abnormalities such as diet, exercise and/or control of diabetes. The eradication of the HCV in these genotypes will not reduce the steatosis.

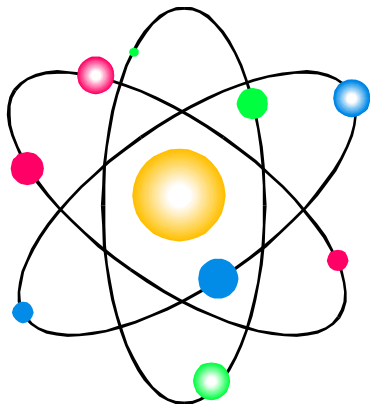
What we know to date about the potential effects of alcohol on patients with chronic hepatitis C is that during the acute infection, alcohol lowers the likelihood of clearance (either spontaneously or with treatment) since alcohol suppresses the immune system. During chronic infection, alcohol increases the likelihood of abnormal liver enzymes, potentially increases viral load and may increase the development of viral quasispecies. During the decades of chronic disease alcohol has been shown to increase liver inflammation, increase risk of developing cirrhosis as well as increase the risk of developing liver cancer. At AASLD researchers (abstract #888) studied the impact of alcohol use on spontaneous viral clearance on a couple of hundred veterans. The results showed that heavy alcohol use lowered the rate of clearance. Interestingly race and age at time of assessment (not age of infection) were not associated with rates of clearance. The results support the idea that alcohol can negatively influence a person's ability to eradicate HCV after exposure. In this study patients with heavy alcohol use (defined by dependency on alcohol or use of alcohol dependence support services) were 50% less likely to eradicate the virus. This may explain the higher prevalence of HCV among persons with a history of alcohol use/dependency. Unfortunately, this study did not address whether alcohol use that is "not heavy" influences the rate of viral clearance. The researchers also looked at the literature to determine whether alcohol use during anti-HCV treatment would have a similar effect on the likelihood of clearing the virus. Recent literature states that not only does drinking during antiviral therapy reduce the likelihood of responding, but also that drinking up to the time of starting

treatment can also influence response rates. In some research findings published in *J Viral Hepatitis*, 2002 (Tabone, M) the researchers found that a 33% SVR was achieved in non-drinkers compared to a 21% SVR in drinkers of less than 3-5 drinks/week PRE-interferon to a 9% SVR in drinkers of more than 7 drinks/day PRE-interferon. Drinkers who were abstinent for ≥ 3 years prior to treatment had SVR's similar to infrequent or non-drinkers.

Lastly there was some very interesting information shared by Dr. Gregory Everson (Abstract 536) on the safety and efficacy of antiviral therapy in patients with advanced liver disease and decompensated cirrhosis awaiting liver transplantation. Safety in this population is a major concern as patients are at a higher risk of bacterial infections, as was reported by Hoofnagle, 1989, as well as the fact that there was a very high rate of adverse events reported in one study of patients awaiting liver transplantation (23 adverse events among 12 patients treated) reported by Crippen et al, *Liver Transplant* 2001. It is important to remember that pre-treatment eradication of the virus may reduce the risk of hepatitis C after transplantation plus interferon may improve the health of the liver during the waiting period (not a parameter of this study). The researchers developed a LADR (low ascending dose regimen) protocol which consisted of 1.5MU interferon (IFN) TIW (three times a week) plus ribavirin (RBV) 600mg QD. After 2 weeks the interferon was increased to 3MU and then after 4 weeks the RBV is increased by 200mg weekly. Granulocyte Colony Stimulating Factor (G-CSF)/erythropoietin (Procrit) were used to keep PMN (polymorphonuclear leukocytes - neutrophils) >800 , Hgb (hemoglobin) >10 . The goal of the escalation is to get patients to IFN 3MU TIW and RBV 1-1.2g/day. Of the 102 patients enrolled into this protocol, 6 were early drop outs. The SVR by genotype was 11% for genotype 1 and 50% for genotype non-1. What was most impressive about this study is that 32 patients in this group were then followed through transplantation (10 patients were HCV RNA negative prior to transplant and 22 patients were HCV RNA positive prior to transplant). Of the 10 patients that were HCV negative prior to transplantation, 100% remained HCV RNA negative after transplantation, whereas all those

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