

HCV/HIV Today

November 2004

Volume 5, Issue 6

HCV/HIV Today
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Getting and Keeping Life and Disability Insurance

By Mark Scherzer, Esq. *Positive Options* ©1995

New York is one of the states which require health insurers to sell their policies to everyone, regardless of their health status, and does not allow premiums to be calculated on the basis of the health of the insured.

Unfortunately, this policy does not apply to life insurance and private disability policies. Insurance companies do not have to, and generally do not choose to, sell individual policies to persons with serious health risks, such as hemophilia or HIV.

Life Insurance

It is hard to buy life insurance without answering questions about your health; lying is not recommended. The better route is to work for an employer who provides group coverage with no questions asked. As soon as you start a job, read the summary plan description or benefits book your employer is required to give you, to find what coverage is offered. If you've lost your copy, ask the personnel or human resource department for another. There may be an eligibility deadline. Read everything sent to you carefully, in case you are being offered a chance to increase your benefits. In most cases, when you leave a job where you have group life coverage, you have the right to convert to an individual policy, also without

health questions, within 31 days of termination of your eligibility for the group. As you move from job to job, you may build up a number of life insurance policies.

If you already have a life policy, it will not become invalid just because you're positive. Read it carefully. You may have the right to increase benefits from time to time without proving good health. If so, pay attention to the deadlines for exercising this right. This, too, may be a good way to get more insurance coverage. It is hard to have too much. By the way, life insurance "with no questions asked," offered in TV ads, are only for a few thousand dollars. It is intended to pay funeral costs.

Disability Insurance

You need to start planning early if you want the benefits to be there if and when you need them. Disability insurance will mail you a check (usually monthly) if you are unable to work because of illness or injury. If you are employed in New York, your employer is required to provide you with some minimal short-term disability benefits—half your income to a maximum of \$170 per week for the first six months you are disabled.

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Guarding Your Liver

HCV/HIV Bites

By Lillian Thiemann. Reviewed by *Acute Hepatitis Management HIV Consumers Report* Vol. 1 No. 2, 2004

Every thing you eat, drink, breathe, and inject passes through and is filtered by your liver. Toxic substances like street drugs, alcohol, paint and chemical fumes, some HIV drugs, and chemicals in food put a strain on your liver and can cause damage that is called hepatotoxicity. Hepatotoxicity reduces the liver's ability to carry out its functions.

Liver disease, often caused by hepatitis and HIV co-infection, has become the leading cause of death for HIV-positive patients. Those with already damaged livers have to be especially careful to protect the liver from further damage because very few HIV-positive people get on the transplant lists for new livers. There just are not enough livers to go around. You can't survive without a working liver, so keeping yours healthy makes sense.

You can measure how hard your liver is working by getting regular blood tests. The higher the enzyme level measured by a (ALT, AST) blood test, the greater the possibility that the liver is being damaged. If your liver enzyme levels are more than five times normal, your liver is considered to be severely damaged. When this occurs, HIV treatment should be stopped or changed.

Blood tests don't always tell the truth: sometimes in people with very damaged livers, the liver enzymes aren't as high as you'd expect because the liver is so damaged it can't make liver enzymes anymore. So watch out for the common warning signs of hepatotoxicity (fatigue, nausea, abdominal pain, jaundice) and contact your healthcare provider if these occur.

Sometimes the anti-HIV drugs are not the cause of liver damage. However, they can indirectly cause it. The risk increases with:

- ◆ alcohol abuse
- ◆ having higher than normal liver enzymes before initiating HIV treatment, and/or

- ◆ taking an HIV regimen with more than one potentially hepatotoxic medication in it. (Treating hepatitis first – or after stopping HIV therapy because of increased liver enzyme levels – may decrease the risk of severe hepatotoxicity)

Some HIV medications are more likely than others to cause problems with the liver. A "black box warning" is a warning regarding special problems associated with a prescription drug. The Food and Drug Administration (FDA) requires these warnings to be prominently displayed in the label surrounded by a heavy black line.

The following list gives some guidance into which drugs have been identified as more likely offenders to the liver:

- Viramune (nevirapine) is most likely to cause liver problems. About 12% of patients get elevated liver enzymes. Some develop hepatitis –mostly within the first 12 weeks of use. In rare cases, severe liver damage led to patient deaths. Black box warning for liver toxicity.
- Sustiva (efavirenz) and Rescriptor (delavirdine) are associated with higher levels of liver enzymes.
- Protease inhibitors can cause elevations of liver enzymes. Severe problems are more likely with Norvir (ritonavir), Kaletra (lopinavir + ritonavir) and combinations of Norvir with Invirase or Fortovase (forms of saquinavir). They can occur any time during use of PIs.
- Nucleoside analog reverse transcriptase inhibitors (NRTIs) are associated with a buildup of lactic acid, a waste product. Severe cases of lactic acidosis are linked to the accumulation of fat in the liver, called hepatic steatosis. This rare condition can be fatal. All of these drugs carry a black box warning for lactic acidosis.

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Drug Update: The Old, The New, The Still to Come

By Patrick G. Clay, PharmD.

This summary provides a limited and brief overview of abstracts presented at the 11th Conference on Retroviruses and Opportunistic Infections in San Francisco in February. The focus of this review involves drug interactions between antiretrovirals, agents that might be given at the same time as HIV medicines and pharmacokinetic data that may affect how HIV medicines are given or for those newer agents that are likely to be recruiting for patients in clinical trials in the coming months.

Lexiva + Kaletra—Still A Bad Idea

Dr. Angela Corbett of the University of North Carolina—Chapel Hill presented data that provides more information on the dual detrimental drug interaction that occurs between Lexiva and Kaletra, initially presented by Dr. Angela Kashuba on behalf of the AIDS Clinical Trials Group (ACTG) at the ICAAC conference in September 2003. Dr. Kashuba had shown that when Kaletra and Lexiva were given together, the drug levels for both drugs were significantly reduced—meaning these two drugs could not be taken together. Dr. Kashuba's group also showed that giving more Lexiva and/or Kaletra did not overcome this interaction.

However, Dr. Corbett's group tried to determine if the interaction occurred because of the two protease inhibitors (PIs) being taken at the same time, so they separated the doses by 4 and 12 hours in a group of non-HIV infected volunteers. Eleven seronegative persons took Lexiva and Kaletra at full doses (700 mg + 400/100 mg, respectively) together for 10 days at the same time. They then were randomized to either take their PIs at regular doses twice a day at the same time (0H), twice a day four hours apart (4H) or taking 1400 mg of Lexiva (4 tablets) and 800/200 mg of Kaletra (6 capsules) 12 hours apart (12H). The amount of drug in their blood was then checked after seven days of this new dosing scheme. Dr. Corbett's group found that separating the doses did not improve the Lexiva levels, but did improve the Kaletra levels when the drugs were given twice daily. Even when double doses were administered once daily, the levels were still reduced from historical controls. The authors caution that more research to find out how to dose these two PIs together has to be done and until then, these two medicines should not be used together.

Dosing Agenerase + Kaletra—Trying to Juggle, Walk and Chew Gum All at the Same Time

Dr. Heather Wynn Vezina presented clinical results of dosing alterations done on patients receiving Agenerase and Kaletra (lopinavir/ritonavir). Given the recent data showing lowering of both lopinavir and Agenerase when these agents are given together, but still having patients in clinic on this regimen, Dr. Wynn Vezina measured levels of these two agents and made dose adjustments based on those. Levels at the end of the dosing interval for lopinavir were 2-3 times lower than the manufacturer recommends. Agenerase levels were similar to previous reports when given with 100 mg of Norvir. Still, the doses of lopinavir and/or Agenerase were increased in an attempt to improve the levels. Six patients had an extra one or two lopinavir capsules added to their regimen every 12 hours and 3 patients increased their Agenerase intake by one or two capsules every 12 hours as well. Two patients had both done. Diarrhea forced one patient to reduce lopinavir dosing. Lopinavir dose increases in the 6 patients resulted in improvement of plasma levels and improvement in viral loads and CD4 counts at the 12-week time point. This data, again short-term, demonstrates some utility of TDM (therapeutic drug monitoring) in HIV and how select instances may benefit from use of measuring plasma levels of antiretrovirals.

Caveat Emptor—Buyer Beware

Dr. Scott Penzak of the National Institutes of Health's Warren G. Magnuson Clinical Center presented some important findings revealed when his group decided to test generic anti-HIV medications abroad for how much drug was actually in there. This is vital as many in the world cannot afford the high price for antiretrovirals and seek alternative sources for the drugs—including black market and counterfeit suppliers.

Dr. Penzak's group tested five PIs and Sustiva (efavirenz) obtained from sources outside the United States. Specifically, they tested products from Zambia, South Africa, Lithuania and Jamaica. The tests they used to determine if the medications contained the amount of drug they were supposed to were the

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same used by the U.S. Food and Drug Administration (FDA) and applied to manufacturers selling products here in the United States.

They found that most of the drugs were as labeled, despite some being beyond their labeled date of expiration! Most important of the findings was that across the board, ritonavir-containing products (Norvir) failed to meet the standards. Dr. Penzak's group noted these products arrived without having been stored properly—meaning no refrigeration. Shipping of medicines without proper storage sends an important signal to anyone even thinking about getting their anti-HIV medicines outside of regulated sources—buyer beware!

Dr. Ramachandran also evaluated the quantity of available generic antiretrovirals, but limited his analysis to those agents available from India-based manufacturers (three of them). This group assessed levels of Sustiva, Viramune (nevirapine), Retrovir (AZT), and Epivir (3TC)—but not protease inhibitors as was done by the NIH group. They also looked at the combination pill containing Viramune, Epivir, and Zerit (stavudine)—this is not available in the U.S. and therefore there are no standards to which to compare the concentrations found. These investigators found that the quantity of the single medication in the majority of instances was within the expected range allowed by the FDA (range 0.01-8.3%).

It Keeps Going, and Going, and Going...

How long does Sustiva hang around after it is stopped? The common thinking was that after about one week plasma levels of Sustiva were not detectable. Data presented by Dr. Stephen Taylor of the University of Birmingham showed that may not be the case. Dr. Taylor measured Sustiva levels in seven HIV-positive patients who had to stop taking the medication for various reasons. These patients had levels measured one, two and three weeks after stopping their Sustiva. This study showed 4, 3 and 2 out of 7 patients still had Sustiva present in therapeutic levels one, two and three weeks after discontinuing therapy. Importantly, this did not result in resistance development in these patients.

Along the same lines was a study conducted in non-HIV infected women in the Netherlands and presented by Dr. Muro of Tumaini, Kilimanjaro Christian Medical College. Single-dose Viramune was administered to 44 women. Blood levels were sampled twice weekly for 21 days. Drug was still detectable in 40 patients at

day 11, 28 patients at day 15, 16 patients at day 18, 9 patients at day 21 and still detectable in 7 patients at day 22. There were no predictors for the long duration of drug exposure in this population. This half-life was calculated to be 56.7 hours, or a little more than 2 ¼ days. No resistance data is available as these patients were all HIV-negative.

These two studies provided important data as patients who discontinue Viramune or Sustiva due to side effects may have to wait a little longer before the drug goes away completely. It also questions the amount of time between regimens that may need to take place to avoid drug interactions.

Sustiva Neurologic Side Effects Not Related to Levels

As more information is learned about how the body breaks down anti-HIV agents, correlations to adverse effects are ruled in and out. Sustiva's predominant side effect is neurological toxicity (dizziness, drowsiness, altered dreams, etc.) and a group of researchers from Harvard tried to see if this is related to drug levels. Dr. Heather Ribaud presented on behalf of this group the pharmacokinetics of Sustiva in various patient populations and how levels related to adverse events, outcomes and drug discontinuation. They found no correlation between levels, outcomes and discontinuation rates, however, they did find that non-Hispanic Caucasians got rid of the drug faster and this may result in lower levels in this population. They found no higher rates of drug discontinuation in other ethnic groups, so it is thought that though this difference may exist, it doesn't warrant concern for patients.

Drug Levels of the Newer Agents for HIV: So Far, So Good

The experimental drugs Reverset and SPD754 showed encouraging results to date.

Reverset

Dr. Robert Murphy of Northwestern University School of Medicine presented pharmacokinetic information on Reverset (RVT, D-D4FC), a new once-daily nucleoside drug being studied by Pharmasset, Inc. Thirty HIV-positive patients were given this drug as monotherapy in a dose escalating trial. Patients were assigned to receive 50, 100 or 200 mg for 10 days. After 10 days of therapy, viral loads were decreased in all three groups with the 50 and 100 mg groups reporting drops of (on average) 1.67 and 1.8 log₁₀ copies/mL, respectively. Dr. Murphy reported no significant adverse events, but cautioned this is a short-term study and longer studies in combination and in treatment-

experienced patients need to be conducted prior to being made more widely available.

SPD754

Another group of researchers working on the twice-daily nucleoside SPD754 in combination with Efavirenz had their data presented by Dr. John Bethell. These investigators looked at how SPD754 and Efavirenz impacted each other in the plasma and inside the cell (remember, it is inside the cells—CD4 and others—where these drugs have to work). Twenty-one non-HIV infected individuals took 600 mg SPD754 twice daily with or without 300 mg Efavirenz once daily for four days. This duration is considered acceptable as neither of these two drugs is expected to accumulate to any great extent in the body of cells over time.

What Dr. Bethell showed was a lack of interaction when the plasma levels of these drugs are examined. However, when the intracellular levels of these agents were looked at, a significant reduction of SPD754 was seen when it was given with Efavirenz compared to intracellular levels when these agents are given alone. This has significant ramifications in that these two agents will likely not be able to be co-administered (much like Zidovudine and AZT cannot be given together). It also reinforces that intracellular pharmacokinetic drug interaction studies should be conducted with all new (and existing!) agents to maximize understanding of these agents before they are given to patients.

Of course, this is meaningless if the drug doesn't affect those with HIV. Dr. Collins of Shire Biochem presented clinical findings of SPD754. Sixty-three patients were given SPD754 as monotherapy in dosing regimens once or twice daily and ranging from 200 to 1600 mg total daily dosing. These HIV-positive volunteers took these doses for 10 days. Viral loads and resistance tests were done after 10 days. In three patients who had baseline mutations that would have limited efficacy of other nucleosides, a strong decrease in viral loads of around one log were seen after this time period. While this data is limited to very small numbers and only for a short period of time, given the need for new agents, it is important for studies to be continued in the population of resistance patients sorely lacking for new agents.

Dr. Adams of Inveresk presented data on the pharmacokinetics—blood and intracellular of SPD754—in the group of 63 HIV-positive patients reported above. What he reported was the preferable accumulation intracellularly when the medication was given twice daily compared to once-daily across all of the dosing arms. Also shown was the possible correlation between blood levels and intracellular levels. This is the first agent to be able to demonstrate this. Other nucleosides and

protease inhibitors have had to rely on something in the cells to get across the cell's membrane where these drugs need to be in order to work. This maybe the first agent that would tell us what is inside the cells by measuring blood levels—a very beneficial aspect if it holds true in repeated studies.

Receptor Blockers: GW873140, SCH C, SCH D

HIV has to connect or bind to the CD4 cell before it can enter and infect the cell. Blocking binding of HIV to the CD4 cell has long been a site for drug discovery. Approaches to this include going after the CD4 cell's surface membrane receptors, CXCR4, CCR5 and gp120. Though these sites for action have long been known, it has only been recently that orally available drugs have been given to humans. These drugs are being referred to as small molecules, attachment inhibitors or receptor antagonists.

GW873140

A drug discovered by GlaxoSmithKline, GW873140 is designed to impede viral entry by affecting the receptor CCR5. Dr. Piscitelli of GlaxoSmithKline presented the first human pharmacokinetic data of this compound. Seventy non-HIV infected persons (57 males, 13 females) were administered single doses escalating from 50 mg to 1200 mg. This was followed by administering the drug twice daily in doses ranging from 200 mg to 800 mg for seven days. Though plasma levels were obtained after the multiple dosing studies, with these drugs what is important is what percent of the CCR5 receptors are occupied—which were also done. Overall, the drug was well tolerated by the volunteers with some mild gastrointestinal side effects. From the plasma levels, dietary factors are going to be important with this drug as levels went up around two times when given with food. For the percent of receptors bound while taking the medicines, 97% of the CCR5 receptors were occupied 2 and 12 hours after the drug was taken in the multiple dosing studies. This very preliminary information is good news, as these novel approaches to therapy may prove the most effective yet—but only time and properly conducted studies will tell.

SCH D

Schering-Plough also has developed two blockers of CCR5 called SCH C and SCH D and their data was presented by a group of researchers led by Dr. Shurmann. SCH D is being pursued for further development due to its higher activity compared to SCH C. This agent was administered to 48 HIV-positive per-

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sons, who had to have been off their antiretrovirals for at least eight weeks and have a CD4 count at or above 200 cells/uL, in doses ranging from 0 to 50 mg twice daily for 14 days. After 14 days of dosing, decreases in viral loads ranged from 1.08 to 1.62 log with a trend reflecting increasing doses of SCH D. Viral loads rapidly returned to baseline after discontinuing the medication.

BMS 488043

Dr. Hanna presented Bristol Myers Squibb's small molecule, BMS 488043, that is has developed to target the gp120 receptor on the CD4 cell's surface. Though this drug has been studied in dose ranging studies before, more focused dosing strategies were shown. Thirty patients were assigned to get, as monotherapy, either 800 mg (12 persons, 3 placebo) or 1800 mg. Only the 800 mg data was presented. These 12 HIV-infected patients had a mean decrease in viral loads after 14 days of dosing of 1 log₁₀ copies/mL. A significant increase in CD4 counts was seen (106 cells/ μ L) in the BMS488043 group compared to placebo. Importantly, no serious adverse effects were seen and no patient had to be discontinued due to side effects.

The pharmacokinetic studies done in non-HIV infected persons over 14 days of this molecule were also presented by Dr. Hanna during a different session. Comparisons of blood levels of this agent when given with or without food showed that improvement was seen when it was given with food—3-5 times as much of the drug was in the body. There was no difference seen when the drug was given with a low-fat versus a high-fat meal, thus it seems instructions for this agent would be to take with food. Total drug exposure of the body to this drug was increased by Norvir by 43%—what that means now is unknown. Also presented by this data was the likelihood of this agent being dosed at 800 mg twice daily, as it would provide sufficient blood levels to suppress viral replication.

These three studies show that progress is being made in exploring new targets for HIV therapies. It is important to realize all of the data presented is short-term, limited numbers and in non-infected populations at times. Despite this, these results are encouraging for continued pursuit of these agents in combination trials for longer durations of time.

HCV/HIV Bites!

Momma Always Said to Take Your Vitamins!

Researchers from the University of California presented data on the ability of a micronutrient supplement to improve peripheral neuropathy symptoms related to Videx (didanosine) or Zerit. Forty patients took either a vitamin supplement containing L-carnitine, n-acetyl cysteine and alpha lipoic acid or a placebo twice daily for 12 weeks. Every month the patients returned for assessment of improvement in peripheral neuropathic symptoms and other measures of mitochondrial toxicity. After three months, there was no difference seen between the two arms. What was surprising was the increase in CD4 counts in the micronutrient group versus the placebo. Those taking the vitamin twice daily saw a 26% increase in the absolute CD4 count versus a 2% increase in the placebo group. Dr. Kaiser's group reported failing to meet the primary objective of the study in that no improvement in peripheral neuropathy was seen, but no adverse effects resulted from the additional nutritional supplement and an unexpected increase in CD count was noted.

Neupogen Stimulates More Than Just White Blood Cells

Filgrastim (Neupogen, rG-CSF), the white blood cell stimulator used after transplants and in persons with neutropenia (low white blood cells—a not infrequent complication of HIV and its therapy), was shown to increase viral replication in a study presented by Dr. Rapaport of the University of Colorado Health Sciences Center. In a laboratory setting, cells were exposed to levels of filgrastim that would routinely be used in clinical situations. As the amount of filgrastim was increased, HIV replication increased—similar to the increase seen when IL-2 is given in other viral replication experiments. This research provides an explanation why viral replication may be more likely when patients are given filgrastim to treat incidences of extremely low white blood cells.

COX-2 Inhibitors and CD4—Drug-Disease Interaction?

The commonly used medications for arthritis and chronic inflammatory conditions, Celebrex and Vioxx, were evaluated for their influence on T-cells by Dr. Kvale and a group from the University of Oslo in Norway. Having only 24 persons who had been on these medications (12 in each group) for six months, they compared the changes in T-cells between these persons and those on similar regimens and responses.

Though it was difficult to control for a number of factors only those persons on the COX-2 inhibitors had increases in two components of the T-cells. Again, the data is no “smoking gun,” but they did find that there were small, albeit significant, changes in the CD38 and CD28 sub-fractions of T-cells. Why is this significant? Mainly because it is the CD38 sub-fraction that correlates with HIV progression in patients with detectable viral loads. These investigators plan on evaluating further more patients and for longer durations of time. In the meantime, this would not be cause to consider stopping the COX-2’s or not considering initiating them, only a curious fact that warrants further investigation.

Sustiva, Lipitor and Zocor

Already known is that with protease inhibitors, the only two cholesterol-lowering medicines available for use are pravastatin and atorvastatin. But what about the non-nukes? The AIDS Clinical Trials Group (ACTG) looked at this question in ACTG 5180. Dr. John G. Gerber from the University of Colorado Health Science Center in Denver presented important information on the interaction between either Zocor (simvastatin) or Lipitor (atorvastatin) with Sustiva when given to 27 HIV-negative volunteers. The blood levels of Zocor and Lipitor were measured in patients when given by themselves for three days, then they took Sustiva for two weeks and had Sustiva levels measured. They then restarted Zocor and Lipitor while on Sustiva for another three days and then had the levels measured again.

What they found was significant reduction in levels of both Zocor (60%) and Lipitor (~45%) when given with Sustiva. Those two drugs did not affect Sustiva levels, thankfully. If these agents are being considered in patients with elevated cholesterol and they are also on Sustiva, then higher doses may be needed in order to get an effect. A word of caution—this data showed only short-term exposure and close monitoring of side effects should be done when using these agents in combination. There are a number of labs that can run levels on cholesterol-lowering medicines and this may prove beneficial instead of increasing a dose of either of these agents because a drug interaction is expected.

To Measure or Not to Measure Drug Levels—That is the Question

A poster presented by Dr. Ana Rendon of Hospital Carlos III in Madrid demonstrates the complexity and diversity of using therapeutic drug monitoring (TDM) in patients on antiretrovirals. They looked back at all requests for levels in patients to see why levels were being drawn, and importantly, what is being done with the information given to the provider. Most of the requests resulted from toxicity

with a particular agent that the provider wanted to either rule out or rule in the role of elevated levels of the drug in that toxicity. Drug toxicity represented 59% of requests, with unexpected virologic failure being the reason for 39% and only 2% for drug interactions.

Higher than expected drug levels were found in 37% of patients with suspected drug toxicity, and lower than expected drug levels were found in 42% of patients unexpectedly failing therapy. The researchers found that 32% of patients had levels changed based on TDM (10 dose reductions, 8 dose increases and 2 regimen changes). Of these 20 who changed therapy based on TDM, 16 or 80% achieved their goal (toxicity resolved or improved viral suppression). In 11 patients in whom follow-up levels have been done, all have achieved expected concentrations. This and Dr. Wynn-Vezina’s study are the first data that have shown changes to therapy based on TDM in clinical practice and the results are encouraging. Though retrospective, the positive outcomes support TDM use in select situations and open communication between laboratories running the levels and providers ordering the tests.

Summary

Overall, a busy conference with many ideas tossed around for how to better manage this disease. A number of the newer drugs in development are raising curiosity and how they are studied may alter how we approach treatment in persons acutely and chronically infected. Drug interactions and dosing alterations continue to be discovered and with more information comes a better ability of clinicians to manage patients with less side effects. More data is forthcoming at Bangkok this summer during the World AIDS Conference—so look forward to more summaries from that meeting in the coming months.

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Positively Aware, March/April 2004

Post-Transplant Treatment for Hepatitis C HCV/HIV Bites

Long-term liver damage related to hepatitis C is the most common reason for liver transplants in the U.S. Unfortunately, the hepatitis C virus (HCV) usually reinfects the new liver after a transplant. HCV recurrence typically occurs within a few weeks and sometimes in as little as 24-48 hours after transplantation, following an initial steep decline in HCV viral load. More severe recurrence is associated with high pre-transplant viral load, a liver graft from an older donor, and use of strong immunosuppressive drugs to prevent organ rejection.

Researchers are avidly studying ways to prevent and treat HCV recurrence after liver transplantation. Montserrat Garcia-Retortillo and Xavier Forns reviewed the current state of knowledge in the July 2004 issue of the *Journal of Hepatology*.

The first approach to preventing post-transplant reinfection involves attempting to eradicate HCV before the transplant is performed. If the virus can be completely eliminated from the body, it cannot infect the new liver. Unfortunately, even among people who have achieved a sustained virological response (SVR) to treatment, HCV appears to remain in the body at very low levels. In the June 2004 issue of the *Journal of Virology*, Tram Pham and colleagues reported that HCV genetic material persists in peripheral blood mononuclear cells (a type of immune system white blood cell) for up to five years after spontaneous or therapy-induced HCV "clearance." But because rapid and severe reinfection is most likely in people with high pre-transplant viral loads, any significant reduction in HCV RNA is likely to prove beneficial.

Although HCV therapy can be risky in people with advanced cirrhosis, interferon plus ribavirin is increasingly being used in HCV patients awaiting liver transplants. For example, Gregory Everson and colleagues treated 102 HCV positive cirrhotic patients with interferon plus ribavirin. Although the SVR rate was low (20% overall, 11% for genotype 1), among the 32 patients who underwent transplantation, HCV did not recur in any of those who achieved a sustained response. In another study, Forns and colleagues found that among 30 patients on a transplant waiting list treated with interferon plus ribavirin, HCV did not recur after transplantation in 6 of 9 patients who achieved a virological response, but did recur in all nonresponders.

Adverse side effects are common in patients with advanced liver disease, and in many cases therapy must be discontinued or dosages decreased (although use

of erythropoietin or filgrastim to stimulate production of red and white blood cells, respectively, may allow some patients to stay on therapy). While HCV treatment response rates in this population are lower than those seen in individuals with milder disease, "antiviral therapy is a feasible choice in HCV-infected patients with advanced liver disease," Garcia-Retortillo and Forns concluded.

Another approach is to use immunoglobulin (antibody) therapy starting right before the transplant operation to prevent reinfection of the new liver. In people with chronic hepatitis B, use of an immunoglobulin preparation called HBIG effectively prevents HBV recurrence. In studies to date, similar use of HCV antibodies has not prevented reinfection of the new liver. However, studies have shown that antibodies with neutralizing activity against HCV do exist, and research is continuing with new types of antibody preparations.

A third approach is to treat patients with interferon-based therapy soon after liver transplantation, while their HCV viral load is still low. Among these patients, who are typically taking high doses of immunosuppressive drugs, adverse side effects and treatment discontinuation are common. Although results have been mixed, some studies show that a proportion of patients can benefit from interferon-based therapy started within the first few weeks following transplantation. For example, in a study of 63 post-transplant patients, Vincenzo Mazaferro and colleagues reported SVR rates of 13% among post-transplant patients treated with standard interferon monotherapy and 33% among those treated with interferon plus ribavirin. Studies also suggest that early treatment helps reduce the risk of reinfection.

More commonly, HCV treatment is initiated months or years after liver transplantation, once signs of damage to the new liver are apparent. By this time, patients are usually healthier overall and taking lower doses of immunosuppressive drugs, enabling them to better tolerate HCV therapy. In general, studies have found SVR rates for this population to be around 20-25% using standard interferon plus ribavirin. Rates are somewhat higher using pegylated interferon. In the July 2004 issue of *Liver Transplantation*, for example, R. Todd Stravitz and colleagues reported on a retrospective evaluation of interferon therapy in 23 post-transplant patients with recurrent HCV. The subjects completed at least six months of interferon-based therapy, 83% with Peg-Intron; however, only

four were able to tolerate ribavirin. After six months of treatment, 11 patients (48%) had undetectable HCV RNA; of these, eight (35% of the total) achieved SVR. Liver biopsies performed two years after HCV became undetectable showed decreased necroinflammatory activity, and 6 of 11 patients showed histological improvement on follow-up liver biopsies. Although SVR rates for transplant recipients are lower than those seen in non-transplant patients, treatment can keep HCV under control in some individuals, and those who respond may experience decreased fibrosis progression.

Caution is necessary, however, because interferon therapy appears to increase the risk of liver rejection. In the same issue of *Liver Transplantation*, Sammy Saab and colleagues reported that five of 44 liver transplant recipients treated with interferon (11.4%) developed acute liver rejection, a rate higher than that seen in liver transplant patients not receiving interferon. These five started interferon an average of 42 months (and up to 83 months) after transplantation, and were treated for an average of three months before rejection set in. Three were successfully treated with intensified immunosuppressive drugs, one required a second liver transplant, and the fifth died from sepsis. In Stravitz's study, eight (35%) of the 23 transplant recipients treated with interferon showed evidence of liver rejection and two required a second transplant. Further study is needed to determine the best immunosuppressive regimens for post-transplant patients with HCV. Whenever transplant recipients are treated for hepatitis C, care must be taken to minimize interactions and synergistic side effects between HCV therapy and immunosuppressive drugs.

As is true for all individuals with HCV, post-transplant patients do not need to be treated until they show signs of liver disease progression. "Given the low efficacy and poor tolerability of current antiviral therapy," Garcia-Retortillo and Forns recommend that "treatment should probably be reserved to those individuals in whom disease progression is well documented." However, liver damage progresses more rapidly in people with compromised immune systems, including those taking immunosuppressive drugs. Martín Prieto and colleagues, for example, found that HCV infection led to cirrhosis in some 30% of transplant recipients within just five years. And in Saab's study, two of the three patients whose acute rejection was successfully treated progressed rapidly to cirrhosis.

For this reason, Garcia-Retortillo and Forns suggest that frequent biopsies are indicated to monitor disease progression in the new liver.

"[A]ntiviral treatment is now fully part of the overall therapeutic strategy post-transplantation," wrote Didier Samuel in an editorial in the July *Liver Transplantation*, but "[t]he timing, the duration of treatment, the use of pegylated interferon instead of nonpegylated interferon, and the optimal dosage of ribavirin are still a matter of debate." As better therapeutic regimens emerge, more research is needed to improve outcomes for liver transplant recipients, who are among the most difficult patients to treat but who can potentially derive considerable benefit from successful therapy.

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How to Start an HCV Support Project: Part 1

HCV/HIV Bites

Ann F. Hirschman, MD, Infectious Disease Chief

Living with hepatitis C is not easy! In order for people with HCV to successfully manage this condition it is important that they receive good medical care and support from as many different areas as possible—medical professionals, family and friends as well as from others living with hepatitis C. Peer support in the form of a support group is one of the critical links in helping HCV positive people face the issues in their everyday lives. Education, support, care and services available to HCV positive people will help them make the best possible choices to effectively manage their lives.

I was diagnosed in 1996 when relatively little was known about hepatitis C. The information on hepatitis C was scarce, with more misinformation than accurate information available. Shortly after I was diagnosed, I asked my doctor to recommend a support group in my area, but to my surprise he told me that there were no support groups in my area specifically geared toward people living with hepatitis C. I did attend a local liver support group that was geared towards any type of liver disease, but I didn't feel like it addressed my specific needs for information and peer support on various issues I was struggling with at that time.

A few months after I was diagnosed with hepatitis C, I began interferon monotherapy. It became clear to me early into treatment that I was not prepared to deal with the physical and psychological side effects related to interferon treatment. I became anxious and depressed! Worst of all I did not recognize the subtle changes in my personality. I also realized how much I needed some form of peer support to help me through treatment. It was during this period that I made a promise to myself that I would start a support group after I completed therapy. Shortly after I completed treatment, I enlisted help from a friend and we started the first HCSP support group in the area. To prepare for facilitating a support group I took a 3 day course about support group facilitation from a local health agency that gave me some valuable information and resources. It wasn't particularly difficult to set up and maintain a support group, but a lot of what I needed to know specific to hepatitis C was learned by hit and miss, and it would have been much easier had I been able to learn from others who were experienced with running a hepatitis C support group.

The importance of support groups can not be overstated. This article is part one in a series of articles designed to help others start a support group and to

provide some tools to help people in the difficult job of maintaining an on-going support group. This is by no means a definitive guide for starting and maintaining a support group, but I hope it will be a helpful tool for support group leaders to use and for others to take the big step of starting a support group. The information in this article will not be suited for everyone because different approaches may be needed for different populations. Every individual is unique, as is every support group. A support group leader must always consider the members' needs and take every opportunity available to adapt to the individual and group needs.

The Need

Why is there a need for support groups? A person living with hepatitis C must make daily decisions on a variety of issues about hepatitis C. Some of these issues may include disclosure, stigma, disease management, and treatment issues. Peer support is critical in providing needed advice and information to help a hepatitis C positive person successfully live with HCV.

There are generally several major reasons why people seek HCV support groups:

Newly Diagnosed

When a person is newly diagnosed it is usually a life altering event. Being told you have hepatitis C raises many questions:

- ◆ What does it mean to have hepatitis C?
- ◆ Am I going to die soon?
- ◆ What should I tell my spouse, family, employer and co-workers?
- ◆ How do I tell others I have hepatitis C?
- ◆ Do I need to start treatment immediately?
- ◆ How do I protect others from getting hepatitis C?
- ◆ How do I take care of myself?
- ◆ How do I take care of loved ones?
- ◆ What about herbs?
- ◆ What should I avoid - alcohol/ other drugs?
- ◆ How do I cope with a potentially life-threatening disease?

Stigma

Stigma occurs when we attach negative labels to people and make generalizations about certain groups or types of people. Generalizations about people are endemic in our society because we all feel a need to

categorize people and situations in order to make decisions in relation to any group. Some people find it easier to generalize about certain groups rather than to take the time and energy needed to discover and understand the differences that make up individuals. These differences may be due to religious, cultural, physical or even pathological reasons. Negative generalizations on a large scale produce prejudice, in which certain groups or populations in our society become stigmatized.

Stigma has two consistent components—the recognition of different characteristics in groups of people, and the devaluation of another human being. Feeling different is one of the reasons why people seek out support groups—they need to be with like-minded people experiencing similar situations.

Most people who have been diagnosed with hepatitis C face some form of stigma or prejudice in their daily lives. It could be a phrase like "you people," or a slight pause when you divulge your HCV status. Friends may stop calling, employers and co-workers may act differently, or it could be as subtle as a facial expression. In any event, we all know how it feels to be treated differently based on being HCV positive. How you handle the stigma associated with HCV is an important issue because it will greatly affect the quality of life, health (both mental and physical) as well as just about every area of the life of those dealing with this condition.

Stigma and prejudice affect every one differently and could lead to:

- ◆ Withholding HCV diagnosis from family, friends, and co-workers
- ◆ Not seeking medical care for fear of being seen at a healthcare setting by others
- ◆ Loss of employment and livelihood
- ◆ Friends and family may "guard" their children from coming into contact with a person with HCV.

Disease Management

After the shock of being diagnosed with hepatitis C a person will have to make a variety of important decisions in order to manage the disease.

Individuals will seek information and advice about many issues including:

- ◆ Alcohol and other drugs
- ◆ Nutrition and exercise
- ◆ Preventing transmission of HCV to others
- ◆ Medical management
- ◆ Depression and anxiety
- ◆ Herbs, vitamins and other dietary supplements
- ◆ Disability issues
- ◆ Sexual issues

- ◆ Guidance on their everyday lives

Treatment

Issues about treatment are one of the main reasons why people seek out HCV support groups. People come to hear what others have experienced on treatment as well as to learn from others about effective strategies to cope with the side effects of therapy.

Peer support is critical for people taking interferon-based therapy. There are a wide variety of physical and psychological side effects that people may experience on a daily basis. The potential for drug-induced psychological problems is frightening for most people to think about. During HCV medical therapy the side effects can be so subtle that only the people in close contact are able to notice any changes. Support group members who have experience with these side effects are able to help identify and help others cope with these distressing issues.

After Treatment Issues

The side effects of treatment will continue even after stopping therapy. It may take even longer to feel completely back to "normal." The uncertainty of treatment outcome will weigh heavily on most people. Until someone receives the news that their treatment was "successful" or "unsuccessful," they can become quite anxious. In addition, if the hepatitis C virus does come back after enduring a six month or year long therapy it is disappointing and makes it difficult for people to decide how to move forward.

These are some of the most important issues that I have found that have been raised in support groups, but it is by no means the entire list. The amount of support and the different issues raised by hepatitis C positive support group members is truly amazing.

Part two of this article will focus on identifying experts and resources as well as on one of the most important questions to consider: "Why do I want to start a support group"?

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Using Nutrition to Ward Off Side Effects

HCV/HIV Bites

By Carla Heiser, RD and Tom Barrett, MD

Understanding the relationship between food and medicine has been of interest for centuries. The earliest medicines were derived from plants and animals. Digitalis, used in the treatment of heart conditions, is a medicine derived originally from a plant source—foxglove. Pharmaceutical grade (pure) medications were developed to standardize both the quality and concentration of a drug in a medicine. Today Western medicine has grown reliant on pharmaceutical technology to produce drugs that will treat many conditions.

In disease treatment we try to impact biochemical pathways (how medications and foods are processed). We “push” a pathway to produce specific chemical endpoint and to affect metabolism. We can also use what is known about the way medicine and nutrients work together to improve effectiveness and allow the use of lower doses—translating to lower healthcare costs and lower side effects.

However, not all medicines work that way. HIV medications can not be dose adjusted based on diet. Also, in HIV disease nutrient requirements are affected by the disease itself and the interactions of multiple medications. Still, we can minimize side effects and changes in metabolism with diet and nutrient supplements. Medication effectiveness and potency is increased through improved drug absorption and tolerability and less side effects.

Many of these medicines require nutrients to improve results. For example, in the treatment of diabetes there are many medicines that may lower blood sugars and prevent further complications. Proper nutritional intake to correct problems in metabolism and body composition is also necessary. Achieving nutritional health may even erase diabetes completely. However, if a patient does not follow healthful practices, the medicines do not work effectively and the disease progresses.

Some of the diseases that are impacted by the power of food include allergy and food sensitivities, cancer, endocrine disorders, gastrointestinal disease, other infectious diseases beside HIV, hormonal imbalance and neurological disorders. Specific conditions where diet composition are crucial include co-therapies for treating high cholesterol, diabetes, high blood pressure, birth defects, learning disabilities, heart disease, and even Alzheimer’s disease. There also is a growing body of evidence that nutritional strategies play a direct role in disease prevention.

Consider that the human body is like a Corvette. Putting diesel fuel into the gas tank should be unthinkable. Similar to a high performance vehicle, our bodies convert food into energy. Foods that contain highly processed sugars and bad fats are “improper” fuel. Our body is unable to convert these foods into energy efficiently. Pathways are diverted to fat storage. Not only does this scenario promote obesity and obesity-related disease, but it also leaves our “gas tank” low on fuel, and we become deficient in energy and nutrients.

Studies show that the standard American diet is sub-standard in basic nutrients—including vitamins, minerals, anti-oxidants and fiber. Diets are commonly deficient in essential and healing fats and oils, like flax, borage, evening primrose and fish oil. On the other hand, the intake of other nutrients such as simple sugars (table sugar, juices, sodas and white refined starches) and processed hydrogenated or highly saturated fats (fats that are hard at room temperature, such as chicken skin and white fat marbled in meats) is excessive.

In our medical practice we seek to improve the nutritional value of a patient’s diet as an adjunct therapy to primary care. Our clinical nutritionists teach strategies to improve disease-reducing complications and medication side effects. Most notable is the impact of nutritional approaches to control diabetes, high blood pressure, high cholesterol, and gastrointestinal or stomach problems. Fatigue, hormonal imbalance and pain management also respond well to holistic care approach.

Messages to consumers and patients are misleading. Yet the bottom line is simple—eat wholesome food, including the proper fats and oils. Limit junk food and bad fats.

Perhaps the most important thing for our patients to do is to keep an open mind about the process. Often patients have the idea that they will never have another French fry again. They are frequently surprised by the variety of foods that we recommend including in their diets.

Carla Heiser, MS RD, LD and Tom Barrett, MD specialize in caring for people with HIV at the Howard Brown Health Center in Chicago, established to serve the city’s gay, lesbian, bisexual and transgender community. Visit www.howardbrown.org.

Contributing authors Jennifer Zawaski, RD, LD and Emily Lindner, MD also work for Howard Brown. Contributing author Judith A Ernst, DMSc, RD is an Associate Professor of Nutrition and Dietetics for the School of Health and Rehabilitation Sciences at Indiana University School of Medicine. Heiser is also the president of the Center for Functional Nutrition at Advocate, Illinois Masonic Hospital in Chicago. The authors are on staff at the Center. Visit www.ics.meta-ehealth.com. Online assessment and nutritional intervention is available, as well as recommended supplements.

The following are examples of our medically supervised recommendations.

Overall Nutritional Guidelines (for non-vegetarians)

- Include a quality assured (see below), potent multivitamin and mineral supplement daily.
- Eat natural, whole foods, the less processed, the better
- Limit simple sugar and refined white carbohydrates
- Use 100% whole grains in moderate amounts divided over meals and snacks
- Use lean, hormone-free meats, poultry and eggs
- Eat cold water fish 3-5 times a week (wild salmon, canned salmon or yellow fin tuna)*
- Eat plenty of fresh or frozen vegetables
- Include low-sugar, high-fiber fruits (apples, pears, berries, cherries, citrus)
- Use teas or coffees that are organic (processed by water, not chemicals)

Nutritional Protocol for Treating Diarrhea and Other Gastrointestinal Side Effects

- Take out offending foods
- Eliminate wheat and gluten-containing foods
- Consider options for replacing cow milk dairy
 - Switch to hormone-free or organic dairy products
 - Consider fortified soy, rice or almond nut milk
- Add soluble fiber
 - Food sources: ground flax meal, 100% whole grains, legumes, peas and lentils, low-sugar fruits (see above) and vegetables
 - Supplements: Metamucil, Citrucel, Benefiber
- Drink plenty of hydrating fluids including water and decaffeinated tea
- Limit, or avoid, caffeine, sodas and alcohol
- Add probiotics (a blend of acidophilus and bifidobacteria)
- For severe diarrhea associated with weight

loss, use L-glutamine up to 30 g (2 Tbsp. Worth) a day in divided doses. **

Nutritional Protocol for Treating High Cholesterol and Triglyceride Levels

- Limit sugar and refined, white carbohydrates
- Include the right dietary fats (avoid processing or high heat): flax/borage oil blend—add to foods or liquids without heating it; cold water fish; olives; avocado; cold-pressed oils (olive, sesame, canola, walnut, sunflower and safflower); raw nuts and seeds; flax meal/oil; raw nut butter (peanut, almond or cashew)
- Eliminate bad dietary fats: saturated animal fats and hydrogenated (trans) fat (typically found in processed, long shelf-life convenience foods like popcorn, crackers, snack cakes, many salad dressings and margarines, etc.)
- Improve dietary fiber intake
- Add quality assured supplements including fish oil, policosanol or non-flush niacin***
- Improve physical activity

Nutritional Protocol for Enhancing Immune Function

- Nutrient-rich, whole foods
- Include the right dietary fats (see above)
- Eliminate bad dietary fats (see above)
- Vitamin/mineral/antioxidant supplementation

Nutritional Protocol for Improving Glucose Tolerance and Managing Diabetes

- Limit sugar and refined, white carbohydrates
- Include the right dietary fats (see above)
- Ensure adequate protein and “good fats”
- Divide meal intake into small portions, eating every 3-4 hours
- Limit starches at meal based on blood sugar levels before and 2 hours after a meal
- Include chromium and vanadium supplement with each meal

Quality assured—look for the Good Manufacturing Practices (GMP) rating on the label, given by the National Nutritional Foods Association (NNFA). NNFA is the oldest and largest non-profit organization dedicated to the natural products industry in the U.S. The “A” rating is given for compliance to rigorous standards. The NNFA’s GMP certification program ensures that all elements of the company’s manufacturing processes meet specified performance standards of each measure, including quality and disease control, cleanliness and training, receiving and testing of raw materials, and procedures for storage and distribution. “GMP Certified” is different from “GMP compliant.”

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Researchers Identify Better Hepatitis C Treatment HCV/HIV Bites for People with HIV

The preferred treatment for hepatitis C, peg-interferon and ribavirin, is safe for people who are also infected with HIV, according to a new study in the July 29 issue of "The New England Journal of Medicine." Moreover, this treatment proved superior for the treatment of hepatitis C virus (HCV) in HIV-coinfected persons when compared with the previously accepted treatment, standard interferon and ribavirin.

The study compared the effectiveness of two forms of interferon: a once-weekly dose of peg-interferon and standard interferon taken three times weekly. Peg-interferon with ribavirin is currently the approved treatment for hepatitis C in persons without HIV. Prior to this study, limited data were available on the benefit and safety of peg-interferon and ribavirin in HIV-infected people.

The study was funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Center for Research Resources (NCRR), both parts of the National Institutes of Health (NIH). NIAID's Adult AIDS Clinical Trials Group conducted the study at 21 research centers in the United States.

"We are pleased to see such a clear and definitive result from this study," says NIAID Director Anthony S. Fauci, M.D. "Just a decade ago treatment of HCV in persons infected with HIV was not a priority because they died from AIDS before developing serious complications of hepatitis C infection. As new anti-HIV drug treatments extend the lives of HIV-positive individuals, studies like this one provide essential guidance on treating other serious health problems affecting people living with HIV."

HCV is primarily spread through infected blood. Most people with the virus have no signs of illness, but in some the infection progresses to chronic liver disease, liver failure or liver cancer. The disease progresses more rapidly in people who have HIV.

The Centers for Disease Control and Prevention (CDC) estimate that HCV infects about 25,000 Americans annually and is responsible for about 8,000 to 10,000 deaths per year. About 3.9 million Americans have been infected with HCV, 2.7 million of whom are chronically infected, according to the CDC. It is also estimated that of the 1 million HIV-infected Americans, about 300,000 are also infected with HCV.

"We carefully monitored the study volunteers for side effects. Most tolerated the treatments well, and relatively few discontinued therapy prematurely. We were also encouraged that HIV infection remained under control during the study," says Raymond T. Chung, M.D., lead investigator and director of the Center for Liver Disorders in the Gastrointestinal Unit at Massachusetts General Hospital.

The 133 HIV-positive study volunteers were randomly assigned to take peg-interferon or interferon for 48 weeks. All study volunteers also took ribavirin, an antiviral drug that is also part of standard therapy for hepatitis C. Study volunteers who completed the treatments – 16 withdrew early for various reasons – were followed for 24 more weeks to evaluate long term treatment success.

In the group that took peg-interferon, 27 percent of patients had no detectable HCV in their blood 24 weeks after completing treatment (sustained response). In contrast, of those who took interferon, only 12 percent had a sustained response. Importantly, more than one third of those volunteers who failed to clear HCV appeared to experience improvement in their liver biopsies, suggesting the treatment was beneficial in this group as well. Researchers also found that the volunteers whose HCV levels failed to fall substantially within the first 12 weeks never experienced a sustained response.

NIH News

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EMBARGOED FOR RELEASE
Wednesday, July 28, 2004
5:00 p.m. ET

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Update from DDW: Part 3

Alan Franciscus, Editor-in-Chief

The final report on the DDW 2004 conference will focus on various reports issued, including practice patterns of liver specialists in the United States, managing treatment related anemia and the effect of estrogen replacement therapy on treatment outcome.

Practice Patterns

Sean P. Hurley and colleagues studied the practice patterns of gastroenterologists and hepatologists to assess whether clinicians followed an acceptable approach to treatment and management of treatment side effects. In this national study, 5000 gastroenterologists were mailed a 31 question survey of whom 17.8% responded. It was generally found that most clinicians followed established management patterns but there were still many who did not. In 77% of respondents the therapy of choice was pegylated interferon plus ribavirin, the current standard of care. Seventy-five percent of the respondents followed the 12 week rule and discontinued medical therapy in patients who did not achieve a 2 log or greater reduction in viral load.

Key Points:

- ◆ Initially 45% of physicians would dose reduce HCV medications to manage severe fatigue and cytopenias (blood disorders).
- ◆ Growth factors were used to manage side effects, but insurance reimbursement limited the use of growth factors more than 50% of the time in 14% of the respondents.
- ◆ Twelve percent would use pharmaceutical agents to treat muscle/joint pain and fatigue.
- ◆ Thirteen percent would start patients on antidepressants before treatment.
- ◆ Most (74%) would manage interferon induced depression themselves with SSRI's, listed as the treatment of choice.

Of interest, the researchers found that physicians in high-volume practices were less likely to dose reduce or discontinue therapy when managing treatment side effects. Finally, the researchers reported that according to their study patients were less likely to complete therapy when a physician used a dose reduction approach to manage fatigue and cytopenias.

Treatment Induced Anemia

Ribavirin is associated with a hemoglobin (Hb) decline which may require the use of adjunct therapies or a reduction in the ribavirin dose.

Anouk T. Dev and colleagues reported on a study they conducted to find out if the drop in Hb is predictive of sustained virological response (SVR). In this retrospective study, the investigators identified 349 patients from two hospital databases. Hb levels were measured at baseline, and at weeks 4 and 8 of therapy. No patient in this study had a ribavirin dose reduction during the 8 week period.

The patient characteristics in this study were: male (75%), genotype 1 (83%), Caucasian (66%). Sixty two percent received pegylated interferon plus ribavirin and 38% received standard interferon plus ribavirin.

The authors reported that an Hb drop of 3g/dl levels or more occurred in 32% of the patients during the first 8 weeks of therapy. But it was found that a decline in Hb during the first 8 weeks of combination therapy is not predictive of an SVR. Further studies are required to assess whether longer initial levels of Hb affect treatment response, including early and sustained virological response.

In another report, long term use of epoetin was studied. In this study conducted by Paul Packros and colleagues, 185 patients who developed anemia during therapy were randomized to receive either once-weekly epoetin (93 patients) or a placebo (92 patients) during the first 8-week double-blinded phase of the study. After the double-blinded phase of the study was completed, all patients received epoetin for the remainder of their treatment. Patient characteristics were similar in the two groups.

The authors found that 84% of the total patient population in this study maintained their ribavirin dose and that epoetin therapy was well-tolerated and maintained over the entire course of HCV therapy. Furthermore, it was found that the use of epoetin did not adversely affect HCV clearance. The authors also noted that more studies are needed to determine whether maintaining higher ribavirin doses with epoetin increased sustained virological response rates.

Improving the efficacy of epoetin alfa was the objective of a retrospective study conducted by Aijaz Ahmed and colleagues. In this study, the medical records of 56 consecutive patients with HCV who were treated with weight-based ribavirin dosing and peginterferon alfa-2a or peginterferon alfa-2b were analyzed. The patients were identified during a 12 month period between 6/1/02 and 6/1/03 at a university hospital satellite clinic. Pa-

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tients with pre-existing anemia, platelet count less than 50,000, or decompensated cirrhosis were excluded. Baseline blood counts were obtained and a weekly complete blood count performed for the first 12 weeks of treatment. New onset of anemia was defined as hemoglobin less than 12 g/dl, hemoglobin decline more than 3 g/dl or hemoglobin decline more than 2 g/dl with significant fatigue. Patients with new onset of anemia were treated with epoetin alfa 40,000 units/week until 2 weeks after their counts returned to baseline. Patients treated with 40,000 units/week who developed severe anemia (10-11 g/dl) were prescribed 60,000 units/week until their hemoglobin levels returned to baseline.

Four patients out of the 56 patients were excluded from the study data due to failure to complete 12 week of treatment. Of the 52 remaining patients, 34 met the study criteria for therapy-related anemia. Thirty of the 34 patients were treated with epoetin, of whom 90% were managed on 40,000 units/week and 10% required higher dosing of epoetin at 60,000 units/week. Seven percent required additional supplementation of ferrous sulfate (iron-deficiency anemia). Twelve percent were dose reduced because they did not qualify for insurance coverage of epoetin. An additional 7% of patients required ribavirin dose reduction of 200 mg due to delays of insurance authorization and delivery of the drug.

The authors found that the average patient developed anemia during the first 12 week period. As expected there were no complications associated with epoetin treatment during the study period.

The authors concluded that early identification of treatment-related anemia can prevent ribavirin dose reductions, which should increase the percentage of patients who stay on HCV therapy and thereby increase the chances of a successful treatment outcome.

The authors made the following recommendations which they considered crucial to improving the efficacy of epoetin:

- ◆ Weekly complete blood counts
- ◆ For those patients identified as anemic, folate and iron studies
- ◆ For those patients identified as anemic, repeat complete blood counts weekly to follow progress on epoetin alfa and identify those that may need higher doses of epoetin alfa
- ◆ Ferrous sulfate for those with low iron on iron studies
- ◆ Insurance carrier policies on the use of epoetin alfa

- ◆ Nursing staff familiarity with use of epoetin alfa, criteria for its use in patients with ribavirin and peginterferon related anemia, as well as familiarity with requesting insurance authorization for epoetin alfa.

Estrogen Replacement Therapy

It has been suggested that women (especially premenopausal) respond better to interferon based therapies than men. It has been speculated that estrogen may improve treatment outcome because of its immunomodulatory properties. In order to test this hypothesis, Matthew J. Hepburn and colleagues retrospectively analyzed data from five multi-center treatment studies. All patients included in the analyses were previously treated with weight-based ribavirin plus standard interferon or pegylated interferon. The medication lists for all women over 45 years old were reviewed for oral or transdermal preparations of estrogen. Women over 45 years old receiving estrogen replacement therapy (ERT) were compared to women not receiving ERT. A total of 179 women over 45 years old were available for analysis. The patient characteristics were similar between both groups.

The authors reported that no differences existed in treatment outcome with or without ERT, except that treatment response in patients treated with pegylated interferon were higher in the group of women who were not receiving ERT. The authors concluded that ERT appeared to have little impact on the response to HCV treatment outcome and that there may be another cause which may explain the higher treatment response rates among pre-menopausal women.

However, the authors also pointed out that there were limitations in their study design:

- ◆ ERT compliance was not monitored
- ◆ Other factors that may influence response to therapy were not controlled
- ◆ Data was measured across different trials
- ◆ The definition of post-menopausal women (age greater than 45 yo) was imprecise.

The DDW is the Digestive Disease Conference held in New Orleans, LA. This article was reprinted with permission from HCVAdvocate.

The Treatment of Experienced Patients and Resistance Mechanisms

By Gregory M. Lucas, M.D.

Groundbreaking new clinical trial results were few and far between at the 11th CROI. However, there were several trials worth highlighting related to the management of treatment-experienced patients and a great deal of new data and insights on antiretroviral resistance mechanisms.

Boosted Atazanavir vs Lopinavir in Treatment-Experienced Patients: 48-Week

Follow-up 48-week data from the BMS-045 trial were presented by Edwin DeJesus in a poster session [Abstract 547]. This trial randomized 358 subjects who had failed at least two HAART regimens and were PI-, NNRTI-, and NRTI-experienced to receive 1) atazanavir (ATV) / ritonavir (RTV) (300/100 mg qd); 2) lopinavir/ritonavir (LPV/r, 3 tablets bid); or 3) ATV (400 mg) / saquinavir (SQV) (400/1200 mg qd) each in combination with an NRTI backbone. Twenty-four-week data from this study garnered considerable attention at last year's IAS conference in Paris [Bardo et al., Abstract 118 2nd IAS, Paris, 2003], as ATV/RTV performed as well as LPV/r in this experienced study population, results that have been upheld by 48-week data presented at CROI. In an intent-to-treat analysis, 56% and 38% of patients randomized to the ATV/RTV arm achieved a VL <400 c/mL and <50 c/mL, respectively, compared to 58% and 46% of those in the LPV/r arm (differences not statistically significant). The efficacy of the ATV/SQV arm was inferior, as it was at 24 weeks. Increases in total cholesterol and triglycerides were significantly higher in the LPV/r group than the ATV/RTV arm, and more patients in the LPV/r arm were treated with lipid-lowering drugs (19% vs 12%, $P < 0.05$).

It should be noted that the participants in this trial were not highly treatment-experienced, and these results should not be extrapolated to true "salvage" situations. Extrapolation to PI-naïve patients may be appropriate, however. The results of BMS 045 will undoubtedly increase enthusiasm for the use of ATV, and especially RTV-boosted ATV, as a first-line PI.

You Don't Need Suspenders if You're Already Wearing a Belt

Scott Hammer presented results from the ACTG 372A study, showing that intensification with abacavir (ABC) provided no benefit in patients whose viral loads were already suppressed on a 3-drug HAART regimen [Abstract 56]. A total of 229 AZT-experienced participants who had achieved VL <500 c/mL in the parent study with indinavir (IDV) and 3TC plus either AZT or d4T were randomized to add ABC 300 mg bid or placebo. Over a median follow-up of 4.4 years, the composite endpoint of virologic failure or treatment discontinuation was reached by 53% in the ABC group and 55% assigned to placebo. In secondary analyses, there were also no significant differences between the groups in rates of virologic failure alone, episodes of intermittent viremia >50 c/mL (blips), or low-level viremia measured using an ultrasensitive viral load assay with a limit of detection of 6 c/mL. It should be noted, however, that intensifying successful regimens is not often done, whereas there is some support for intensification strategies in patients with persistent low level viremia on HAART [Katlama C, et al. *AIDS* 2000, 14:781 and Schooley RT, et al. *AIDS* 2002, 16(9):1257].

3TC Forever?

Several rationales have been proposed over the years for continuing 3TC in the regimens of patients with known or suspected 3TC-resistance. The M184V reverse transcriptase mutation decreases viral fitness and antagonizes the development of thymidine analogue mutations (TAMs), K65R, and Q151M. Moreover 3TC is almost universally well tolerated, has a low pill burden, and does not appear to contribute to mitochondrial toxicity. The COLATE trial addressed the question of whether continuing 3TC after 3TC failure is beneficial [Abstract 549]. One hundred thirty-one subjects who had a VL >1,000 c/mL on a 3TC-containing regimen (91% had M184V at study enrollment) were randomized to either continue or discontinue 3TC in an open-label format. Subjects' clinicians chose a regimen consisting of at least 3 drugs prior to randomization; the mean number of drugs, excluding 3TC, remained

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similar in the two arms over 48-weeks of follow-up. There were no differences in the average change in viral load (-1.4 log₁₀ c/mL with 3TC vs. -1.5log₁₀ c/mL with no 3TC) or in viral load <50 c/mL at week 48 (52% with 3TC and 44% with no 3TC). The authors concluded that the trial showed no evidence that continuing 3TC in the setting of known or suspected 3TC resistance provides benefit.

Notably, some drugs (like ABC and ddl) can maintain M184V, and the lack of difference between the study arms might be explained if M184V, and its purported beneficial effects, were maintained in the group not receiving 3TC. However, this did not appear to have occurred to a great extent: M184V was detected in over 80% of participants who experienced virologic failure in the 3TC arm during follow-up, while less than 20% of those failing therapy in the non-3TC-containing arm had a detectable M184V mutation during the last 6 months of the trial.

Two caveats about this trial should be noted. First, a potential benefit of maintaining M184V with 3TC is thwarting the development of some of the more troubling nucleoside resistance mutations. While this issue will be further explored in the COLATE trial, analysis of mutations other than M184V that emerged during the study had not been completed as of the presentation at CROI. Second, the relative benefit of M184V on viral fitness may be most evident in true salvage situations. The participants in COLATE were not heavily pretreated; nearly 70% achieved a VL <400 c/mL at week 48, and approximately 50% achieved a VL <50. These rates of viral suppression are similar to those seen in ART-naïve trials and may have obscured a modest benefit of M184V on viral fitness.

K65: Balancing the Effects of Mixed Mechanisms

The K65R mutation is a recent upstart in the world of NRTI resistance because of the use of thymidine analog-sparing regimens, and, most notably, the spectacular failures of triple nucleoside HAART regimens that do not contain AZT or d4T (see Gallant JE, "Antiretroviral Therapy: The Naïve Patient", p 1). Considerable attention was focused on the K65R mutation and its mechanisms of action at this year's CROI. In a symposium, Lisa Demeter [Abstract 162] provided an overview of mechanisms of resistance to NRTIs, and U. Parikh [Abstract 54] and K.L. White [Abstract 55] presented oral abstracts focusing on the interactions between K65R and other NRTI-associated resistance mutations.

Thymidine analog mutations (TAMs) cause resistance to NRTIs by increasing the ability of HIV's reverse transcriptase enzyme to excise these agents from transcripts after they have been incorporated, with T215Y being the most efficient (Table). As these mutations accumulate, the result is broad resistance to all NRTIs. In contrast, the M184V mutation potently blocks incorporation of 3TC into growing RNA transcripts, producing complete resistance to this drug (Table). However, M184V also has a detrimental effect (from the point of view of the virus, that is) on the ability of HIV to excise previously incorporated NRTI. M184V also blocks incorporation of other NRTIs, but much less efficiently than it blocks incorporation of 3TC (ABC, ddl >> AZT, d4T, TDF). Thus, in the cases of ABC and ddl, the aggregate effect of M184V's counteracting influence on incorporation and excision is to produce detectable but clinically insignificant loss of susceptibility to these agents. Conversely, in the case of AZT, d4T, and TDF, the aggregate effect of M184V is to antagonize HIV's primary mechanism of resistance to these agents: NRTI excision.

There is a similar trade-off for K65R. In combination, K65R and M184V cause complete resistance to 3TC and substantial loss of susceptibility to ddl and ABC. Interestingly, although TDF plays an important role in selecting the K65R/M184V combination of TDF is much less pronounced, because the decreased incorporation of TDF and the antagonized excision balance out.

The interplay between these two primary NRTI resistance mechanisms was used to explain the nearly universal failure of triple NRTI regimens containing TDF, 3TC plus either ABC or ddl [Demeter LM, et al. Abstract 162]. Emergence of the K65R/M184V combination produces high-level resistance to 3TC, ABC, and ddl, effectively leaving TDF monotherapy. In cell cultures HIV susceptibility to AZT is increased by K65R, and this has been borne out in clinical experience, where K65R is a rare mutation in AZT-containing regimens [White KL, et al. Abstract 55]. Additionally, from a clinical perspective, triply NRTI regimens that contain AZT (or d4T), while not as effective as PI or NNRI-based regimens, are not afflicted by the Achilles heel of non-thymidine-containing triple NRTI regimens (see Gallant JE, "Antiretroviral Therapy: The Naïve Patient", p 1).

It's the Drug Levels, Stupid!

In deep salvage situations, the ability to achieve virologic suppression probably hinges on the ability to overcome existing PI resistance with serum drug concentration. R. Bertz presented preliminary results

from the ABT 049 study, in which 33 heavily experienced patients were randomized to receive LPV/r (*Kaletra*) 667/167 mg (5 capsules) bid or LPV/r 400/300 mg (3 capsules) bid plus RTV 200 mg bid both in combination with 2-3 NRTIs selected by participants' clinicians [Abstract 134]. LPV trough levels were similar in the two arms and 60% to 70% higher than those historically seen with regular LPV/r dosing. Viral suppression was similar in the two arms, but there was a trend toward better tolerability in the arm containing 5 LPV/r capsules than in the arm with extra RTV. In a multivariate analysis both the LPV inhibitory quotient (IQ, defined as the LPV trough divided by the protein-binding adjusted IC50 for the subject's particular HIV isolate) and the number of active NRTIs in the regimen were strongly associated with the log10 decline in viral load on therapy as well as the likelihood of achieving a VL<400 c/mL.

Of course toxicity is the other side of the double-edged sword when attempting to increase drug concentrations. For example, IDV concentrations have been correlated with nephrolithiasis and cutaneous toxicity. Similarly, Barrios reported that higher ATV plasma concentrations were significantly associated with the degree of hyperbilirubinemia [Abstract 606]. Additionally, considerable attention was focused on efavirenz (EFV) pharmacogenomics, race, and central nervous system side effects. In substudies of ACTG 5095, the trial comparing EFV/AZT/3TC/ABC, EFV/AZT/3TC, and AZT/3TC/ABC (the latter arm discontinued due to high failure rate), EFV clearance and central nervous system side effects were found to be strongly associated with a CYP2B6 polymorphism (the cyto-chrome P450 enzyme most directly involved with EFV metabolism) an allelic variant that is more common in blacks than whites [Haas D, et al. Abstract 133]. These differences

may explain the significantly higher drug concentrations) in blacks and Hispanics than in non-Hispanic whites in the ACTG 5095 sub-study [Ribudo H, et al. Abstract 132].

Conclusion

Forty-eight-week data from BMS 045 continued to show similar virologic efficacy of ATV/RTV and LPV/r in treatment experienced patients, with better lipid parameters in the former group. This suggests that boosting drug concentrations well above the viral IC50, reasonable dosing and pill burdens, and tolerability are the main factors currently driving the overall *effectiveness* of PI-based regimens. Adding ABC to IDV-based regimens was not associated with any durability benefit in patients with suppressed viral loads, and continuing 3TC in the presence of M184V was not associated with benefit in minimally to moderately antiretroviral-experienced patients initiating a salvage regimen. Finally, additional basic science and clinical research has shed light on the K65R resistance mutation and how its effects on NRTI incorporation and excision lead to different net effects for different drugs, particularly in combination with M84V.

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Resistance Mechanisms		
NRTI-Associated Resistance Mutations	Blocked Incorporation of NRTI into RNA Transcripts	Excision of NRTI After Incorporation
TAMS (41, 67, 70, 210, 215, 219)	_____	↑↑
M184V	↑↑ (3TC); ↑ (Others)	↓
K65R	↑↑	↓

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Using Nutrition to Ward Off Side Effects (continued)

HCV/HIV Bites

Few companies allocate the financial resources to independently verify that their GMP programs achieve GMP **certification**.

* Beware of higher mercury levels in other cold-water fish (such as trout, cod and sardines). The wild salmon should be farm-raised from Chile or North America. Don't eat swordfish, King Mackerel or tile-fish.

** L-glutamine is expensive and provided through some public aid formularies. The Houston Buyers Club offers it at a lower price. Once you heal the gut

and maintain that with good nutrition, you can lower the dose or cycle on-and-off the glutamine.

*** Non-flush formulation (inositol hexanicotinate) in 500 to 1,000 mg one or two times a day may help avoid flushing. Check with your doctor or pharmacist to see if it's okay to add a baby aspirin before taking niacin to reduce potential side effects. Look for "GMP certified."

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Getting and Keeping Life and Disability Insurance (continued)

If you have earned enough Social Security tax credits (the required credits vary according to your age), you will qualify for monthly Social Security Disabilities (SSD). The Social Security Administration (800-772-1213) will send you a printout with your work history, as well as the amount of money you will get if you are disabled or retire under SSD. The amount depends on how much you have paid in Social Security taxes. Correct any mistakes or give additional information they may not have. It is much easier to do this while you are still working than once you have filed for disability. SSD benefits are enough to make it smart not to work off the books and, if you are self employed, not to go overboard in taking deductions to show low income. It can pay to pay taxes! If you haven't worked enough of the past ten years to qualify for SSD, you will qualify for Supplemental Security Income (SSI). For both SSI and SSD, Social Security has a strict medical definition of disability, but many people with AIDS will qualify.

Unfortunately, these benefits will usually not be enough, on their own, to maintain your standard of living. Even at the top level of Social Security disability benefits you may be hard-pressed to pay rent, utilities, food, transportation, and health insurance premiums and co-payments, let alone go to the movies once in a while. To do better, you'll need a long-term disability sold by commercial insurance companies. That will take some planning.

No commercial insurer in New York will sell you disability insurance if they know you are HIV-positive. If you buy a policy by lying (not easy anyway when the insurer can, and often does, ask you to take a blood test), you may well find the policy declared invalid due to fraud. Instead of the benefits you wanted, you may face a lawsuit.

If you go to work for a larger employer, however, disability coverage is often part of the benefit plan. It may pay up to 70% of your pre-disability income when you have to stop working. You may have options to buy extra coverage, too. If you can pay the premiums yourself, the benefits may then be tax exempt when you get them.

Even small employers can buy group long-term disability insurance with few health questions. If you have influence over these decisions in your place of employment, use it soon. Most policies will not cover pre-existing conditions until you have been insured for a year. You'll want to get coverage in place as soon as possible.

Once covered, you will have to take care leaving or changing jobs. Exercise conversion rights (which are present in a few group policies) if you can. In "conversion", you buy an individual policy when you leave the group. If you can't convert, only go to new jobs where disability coverage is guaranteed so you'll have a source of income and its comforts if you have to stop working.

Be sure not to miss any premium payments; if you do, you may lose your insurance.

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*You must not lose
faith in humanity.
Humanity is an
ocean;
If a few drops of
the ocean are dirty,
The ocean does not
become dirty.
-Mahatma Gandhi*