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Current Review & Update on Hepatitis C & HIV/HCV Coinfection

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This update and review includes information reported at recent Hepatitis Conferences: AASLD (American Association for the Study of Liver Disease, November 2000; June 2001), DDW (Digestive Disease Week, May 2001), EASL (European Association for the Study of Liver Disease, April 2001).

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INTRODUCTION

Similarities and Differences between HCV and HIV

In the past twenty years, two newly described human viruses, the hepatitis C virus (HCV) and the human immunodeficiency virus (HIV) (one infecting the liver and the other critically weakening the immune system) have dramatically awakened our understanding of just how fragile is the relationship between humankind and pathogenic microorganisms. These two viruses are similar in many respects. Both viruses have a single-stranded RNA genome, they both have very high levels of viral replication, they both cause chronic subclinical infection that can persist for many years, and they share similar routes of transmission.

However, HIV and HCV are also different in many respects. One of the most important differences between these two viruses is that HCV does not have a nuclear phase during its replication cycle and it does not integrate into the host genome unlike HIV. Nuclear phase means that the virus goes into the nucleus of the cell. Both HBV and HIV have a portion of the life cycle that occurs in the nucleus, while HCV does not.

HIV can integrate into the host genome and HBV can survive as a closed circular coil (referred to as "ccc"). At least, theoretically it should be possible to eradicate HCV more easily than HBV or HIV. Based on this fact, HCV eradication from the body should be much easier to accomplish than eradication of HIV. With the recent introduction of a new formulation of interferon conjugated to polyethylene glycol, pegylated interferon, many HCV-infected individuals will have the opportunity to be "cured" from HCV infection.

This review will discuss many aspects of hepatitis C virus infection including the epidemiology, pathogenesis, clinical management, treatment, and adverse events associated with treatment as well as the differences between HIV and HCV. Hepatotoxicity secondary to antiretroviral agents, which is clearly an increasing problem in the treatment of HIV-infected individuals is discussed in this issue.

Epidemiology

Epidemiology of HCV/HIV Coinfection

Hepatitis C virus (HCV), a member of the Flaviviridae family, consists of at least 6 genotypes and more than 50 subtypes. Genotype 1 is the most common in the United States and genotypes 2 and 3 are the most common in Europe and Asia. An estimated 3.8 million individuals in the United States, 1.8% of the population, have been exposed to HCV, and 2.7 million of these individuals have detectable HCV RNA indicating chronic viral infection. The virus causes approximately 10,000 deaths each year. HCV has infected an estimated 170 million individuals worldwide, about 3% of the world s entire population, and the virus is the leading cause of liver transplantation. In comparison, HIV has an estimated prevalence of 800,000-900,000 in the United States. It appears that many with chronic HCV alone do not progress to complications, a reasonable percentage with HCV alone may eventually die for reasons completely unrelated to HCV. The risk of cirrhosis in patients with chronic HCV infection is approximately 20% within 20 years and 30% within 30 years, and this condition carries a mortality rate of approximately 2% to 5% a year. For example, the risk of dying 3 years after developing cirrhosis is 6%-15%. Treatment with interferon can stabilize (slow or stop) fibrosis progression despite little or no viral load reduction. Further, HCV-related cirrhosis (HCC) is the leading predisposing cause for primary liver cancer, and following the development of cirrhosis HCC occurs at a rate of approximately 3 -10% per year. So, 3 years after developing cirrhosis the risk for HCC is 9% - 30%.

Based on estimates and projections from Gary Davis (Hepatology, 1998; 28), K. Rajender Reddy (University of Miami) suggested at DDW (Spring 2001) that the disease burden from HCV is likely to rise considerably over the next 10-20 years. His estimates/projections are that the increase in the number of patients with cirrhosis over the next 8 to 10 years could be in the order of 500%, which could cause increasing demands on liver transplantation. The cost of health care is also likely to rise significantly. I presume these estimates do not factor in therapy with pegylated interferon/ribavirin. See section on Liver Transplantation.

HCV can be more of a problem when **coinfection** with HIV is present. Although more studies are needed to better understand the affect of HIV on HCV progression over the longer term and the effect of HAART on liver disease progression, a number of studies show that HIV can accelerate liver disease progression. Liver disease progression can lead to cirrhosis and liver cancer, and acceleration may lead to progression in a shorter period of time. Studies are mixed on the affect of HAART on HCV progression. As you will see later in this report several studies appear to show HAART having a negative impact on liver disease, while other studies suggest HAART may not have such an affect or may slow progression. Perhaps all may be true and it may depend on the patient s situation, health, and history. Recent studies suggest that, in the era of potent antiretroviral therapy, the number of deaths due to liver disease in HIV-1-infected individuals has been increasing. In a cohort of about 4,000 individuals, liver disease was the primary cause of non-AIDS death. In a recently published study that retrospectively examined the causes of death between 1991 and 1998 in HIV-1 seropositive individuals, end-stage liver disease was found to be the leading cause among hospitalized HIV-seropositive individuals. Most of these individuals were HCV-positive.

The prevalence of coinfection appears staggering as it s been estimated that about 30% or more of HIV infected may also have HCV. Perhaps as many as 60-90% HIV-infected persons in the United States and Western Europe who acquired HIV through intravenous drugs are also infected with HCV, since HCV is transmitted by blood just like HIV. In fact, HCV may be more easily transmitted than HIV. It s been estimated that most IVDUs get HCV in their first year of IVDU and therefore are likely to have had HCV for longer than they have had HIV. Considering the percentages of HIV+ IVDUs who are African-American and Latino, coinfection in these communities appears to be a major challenge.

Pathogenesis of HCV

Chronic infection with both HIV-1 and HCV are both characterized by dynamic equilibrium between virus production and clearance. Daily virus production appears high for both viruses: the estimated daily virion production for HIV-1 is 9.3 $\log_{10}$ — 10.2 $\log_{10}$ and for HCV is 11.6 $\log_{10}$— 13.0 $\log_{10}$ (as much as billions of HIV virions and trillions of HCV virions).

Virology: Hepatitis C Genetic Diversity and High Level of Viral Replication Pose a Challenge

At the AASLD HCV Conference recently held in Chicago (June 2001), HCV virology and immunology were discussed by Charles Rice, (Rockefeller University), Particia Farci (University of Cagliari, Italy), and Barbara Reherman (NIH). Rice and Farci discussed hepatitis C viral diversity. Within an individual, the virus exists as a quasispecies (i.e. a heterogeneous population of mutated viral forms). Virus replication is a dynamic process with virion half life of 2-3 hours and a high level of virus replication which contributes to genetic diversity, HCV RNA occurs via synthesis of a complementary negative-strand RNA intermediate and is error prone resulting in the generation of a large number of variants. Such high replication rates and the resulting genetic diversity pose important challenges to the development of an effective vaccine and to effective treatment. Evidence is accumulating to suggest that the diverse genetic nature of HCV may have important biologic & clinical implications for viral persistence, for drug resistance and for vaccine failure. Genetic variability is a critical mechanism for the virus to persist in the host (human) possibly by escaping the immune system. During the acute phase of the infection, approximately 15-20% of individuals will clear HCV, but the factors that determine whether the virus is cleared or persists have not been elucidated. Recent evidence suggests that one important factor is viral diversity during acute infection, such that an increase in diversity is associated with progression to chronicity, while self-limited clearance is associated with a virus that remains stable. These data indicate that the early events of the virus-host interaction may determine the outcome of HCV infection. Farci also stated that patients who achieve a response to interferon therapy with sustained HCV clearance exhibit a significant decrease in viral diversity and in the number of viral strains, with a similar pattern to that seen in patients who spontaneously clear the virus. By contrast, patients who do not respond to therapy show persistence of the original dominant viral strains, suggesting that resistant strains are already present prior to therapy.

Immune Response

The immune response to HCV is yielding important new information regarding host/viral interactions. A broad and strong anti-HCV specific CD4+ immune response is an important determinant

of recovery during the acute phase of HCV and in the prevention of severe HCV recurrence after hepatic transplantation. Vigorous HCV-specific CD8 immunity distinguishes individuals with self-limited HCV infection from individuals with chronic HCV infection. Both CD4+ and CD8+ responses to HCV structural proteins (core, E1, E2) are important determinants of a successful outcome to therapy. HIV may have a deleterious effect on HCV specific immune responses in coinfected patients, which may be one of the reasons why higher CD4+ T cell counts and lower HCV viremia have been associated with improved responsiveness to interferon. See the section below on the effect of HAART on HCV.

Pathogenesis: The central pathogenic mechanisms, whether direct viral cytotoxicity (direct killing of cell by infected virus) or the host s immune response, have not been conclusively established for either virus, although each mechanism has been hypothesized to be important in each viral infection. Infection with HIV results in progressive immune dysfunction, secondary to the continued loss of CD4+ T cells, and the eventual onset of opportunistic infections, as a consequence of immunodeficiency. HCV is a hepatotropic virus, and the principle adverse consequence of HCV infection is the development of liver failure. The symptoms associated with end stage HIV infection result directly from pathogenic infection (i.e. pulmonary symptoms with pneumocystis carinii pneumonia or odynophagia from esophageal candidiasis). In contrast, end stage liver disease in HCV results from hepatic fibrosis, a response that can occur to a variety of insults including viral hepatitis, autoimmune attack of hepatocytes, alcohol abuse, drugs, or metabolic diseases due to an overload of iron or copper. The normal liver contains an epithelial component (hepatocytes), an endothelial lining, tissue macrophages (Kupffer cells and perivascular mesenchymal cells (stellate cells). Stellate cells are the key fibrogenic cell; they become activated, transition from quiescent cells into proliferative, fibrinogenic, and contractile myofibroblasts, in response to hepatic injury of any etiology. TGF-b is the major stimulus for stellate cell production of fibrin.

Several studies have evaluated the determinants of hepatic fibrosis in HCV monoinfected and HIV/HCV coinfected individuals. Poynard et al (1997) found that age greater than 40 years at the time of HCV acquisition, alcohol consumption of 50 g or more and male sex are independently associated with accelerated hepatic fibrosis. Benhamou et al (1999) found that HIV seropositivity and severe immunosuppression (CD4 cell count < 200 cells/mm^3, and alcohol consumption were all associated with a higher fibrosis progression rate in HIV/HCV coinfected individuals. Puoti et al (2001) recently reported an independent association between CD4+ cell count < 500 cells/mm^3 and the presence of fibrous septa (odds ratio, 3.2; P = 0.037). Powell et al (2000) demonstrated an association between individuals who inherit high TGF-b1 and angiotensinogen (AT)-producing genotypes and the development of progressive hepatic fibrosis.

Immunology: Strong CTL Response May Be Needed for Viral Eradication

Barbara Reherman reported that prospective analysis of the cellular immune responses of patients with symptomatic, self-limited hepatitis C demonstrate strong Th1 dominated T cell helper and cytotoxic T cell (CTL) responses in the blood. This cellular immune response was targeted against virus epitopes in all structural and nonstructural proteins of the virus. This is similar to findings in HIV. In other patients, lack of such a response or an inability to maintain it for an adequate time was associated with chronic infection. In chimpanzees the CTL response in the liver cells was stronger when virus was self-contained compared to the development of chronic infection.

Rehermann also reported that HCV specific cellular immune responses are maintained for decades after HCV recovery, sometimes in the absence of HCV-specific antibodies. These type of responses are relevant to the question of whether they may prevent persistent infection after re-exposure to HCV.

It appears that the immune system and its relationship to HCV is obviously not well understood. Reherman reported that in chronic HCV, virus specific T cells were present at low frequencies in the blood, but could be found. HCV specific T cells were more frequently found in the liver. She said the reasons for the relative weakness of the cellular immune response, that is unable to clear the virus, yet strong enough to contribute to chronic inflammatory liver injury, are not known. General immune tolerance or immunosuppression are unlikely to be the cause of HCV persistence since in the absence of liver cirrhosis, the majority of chronically infected patients display normal immune responses against other viruses.

It appears that HIV has a negative impact on the immune response to HCV in coinfected persons. HIV may further impair the immune response to HCV and this may contribute to HIV accelerating HCV progression. The effect of HIV on HCV progression appears very complicated. Some persons have end-stage liver disease or cirrhosis with high CD4s and undetectable viral load.

Reherman reported that HCV specific antibodies are generally detected 7 to 31 weeks after infection and that they are targeted against epitopes in all viral proteins (the immune system mounts an antibody response to HCV). Several studies have described neutralizing antibodies that are targeted against the envelope proteins. However, this may be considered a misnomer since these antibodies really do not neutralize the virus. Recovery from HCV has also been described in the absence of an antibody response to envelope proteins and HCV persistence (chronic infection) without sequence changes in the envelope proteins. Therefore, progression to persistent infection is most likely a multifactorial process depending on many aspects of virus-immune system interactions.

Immune Based Therapy

Ray Chung (Massachusetts General Hospital/Harvard Medical School) suggested at the AASLD meeting in Chicago based on preliminary data that immune therapy may be a viable goal. HCV-specific cellular immune responses might help to contain the virus, but it's also been suggested that the immune response might contribute to liver damage. In analyzing the CD8 mediated immune response, Chung identified and reported on two individuals with a strong and persistent cellular immune response against HCV during chronic infection. Both persons also showed control of viral replication and no evidence of active liver disease. Chung concluded that this suggests that an effective, strong immune response can control HCV and may not cause liver damage, and that these findings provide evidence for a rationale to consider immunotherapy in chronic HCV. In HIV we have been looking for immunotherapy without success but maybe we can have better luck in HCV.

Does HAART Affect Liver Disease Progression in HCV/HIV Coinfected Patients?

The short answer is that the Sterling data described below suggests HAART may accelerate HCV progression if the number of CD4 cells increases sufficiently and HIV is suppressed. Other studies do not address the question as directly but suggest that HAART does not accelerate HCV.

An unanswered question is how HAART affects the liver of the HCV/HIV coinfected person. Opinions on this are mixed. Some doctors and researchers feel that HAART may increase ALT, liver inflammation, and virus activity, but that this may not have much long term clinical significance on fibrosis progression. Obviously, the other side is that the affect of HAART on HCV liver disease may be to accelerate progression. A small French study previously reported that patients taking HAART did not have any faster HCV progression than patients with HCV alone. This has not been confirmed, although other researchers have reported findings suggesting the same.

Although the Sterling study (Richard K. Sterling, MCV/VCU, Richmond, VA, DDW May 2001) discussed below has flaws in its design and analysis, as most studies do, it presents interesting findings. The study is small (n=39), but Sterling finds that patients with undetectable or low viral load and CD4 cell counts above 200 are more likely to have cirrhosis than patients with lower CD4 cell counts or higher viral loads. As an explanation for this observation, Sterling suggests that superior or optimal immune restoration from HAART may adversely impact on HCV disease severity. Another possible explanation is that patients with high CD4's and undetectable viral load were more adherent, and therefore had more HIV drug exposure.

Obviously, the patients with hi CD4s & low viral loads (n=29) received treatment for HIV and were doing well with therapy. As Sterling reports, the mean viral load was 1.3 log and the mean CD4 cell count was 552. The mean viral load in the patients with CD4s <200 was 2.7 log viral load and the mean CD4 cell count was 143 (n=9). The patients with high CD4 cell counts (>200) had been infected with HIV for a longer period of time (10 vs 7.8 years). However, there was no difference in the level of ALT, the percent with normal ALT, serum HCV RNA, the percent with high HCV RNA, and total HAI (Hepatitic Activity Index) comparing those individuals with CD4 cell counts above and below 200 cells/mm^3.

Coinfected patients with >200 CD4 cells were more likely to have cirrhosis (21% vs 0%) than patients with <200 CD4 cells. Although the percent with advanced fibrosis was similar in both groups, no case of cirrhosis was seen in those individuals with low CD4 cell counts. Also, patients with undetectable viral load were more likely to have cirrhosis (25% vs 5%).

The authors suggest that the more advanced fibrosis seen in those with higher CD4 cell counts and HIV RNA below assay detection suggests that immune function may be an important determinant in HCV disease severity. Immune restoration with effective HIV therapy may adversely impact on the severity of HCV disease in HIV/HCV coinfected individuals.

In Maribel Rodriguez study (Maribel Rodriguez, Fundacion Gastroenterologica de Diego, San Juan, PR; Jose F. Rodriguez, Univ of Puerto Rico, San Juan, PR, DDW May 2001), she finds that liver disease progression is faster in HCV/HIV coinfected patients than in HCV monoinfected patients despite the fact that alcohol use was increased in the HCV monoinfected patients (97% vs 65%). She reported that these results could be explained by the higher hepatitis C viral load at baseline (5.67 log vs 5.13 log, ie 467,000 copies/ml vs 132,000 copies/ml) observed in the co-infected patients when compared to the mono-infected patients. I think it s important to bear in mind a limitation of this study. In speaking to the author she said that some patients had undetectable HIV and some patients did not. This creates a question about the findings. If the patients with undetectable viral load or high CD4 cell counts progressed more quickly, as Sterling found, and since Rodriguez did not separate the data based on that it s hard to conclude coinfected progress more quickly. It may be that only those individuals with low CD4 cell counts and high viral loads progress more quickly. As well, in speaking to the study authors, Rodriguez expressed concern that HAART related elevated lipids, insulin resistance, elevated glucose, and other HIV or HAART related negative effects on the liver may worsen fibrosis.

Now, if you look at the study from San Diego described below, they found that having HCV did not negatively impact on the survival of patients with well managed HIV. But this study does not report whether these patients had cirrhosis or not as the study above addresses. So, I don t think the two studies necessarily contradict each other. These patients may have had cirrhosis but may not have died.

At the HIV Retrovirus Conference (Feb 2001), Torriani from San Diego and Spanish researchers (abstract 575) looked at the development of hepatoxicity after starting ART (antiretroviral therapy) for 94 HCV/HIV coinfected patients compared to 94 HIV infected patients. They reported hepatotoxicity was correlated with immunologic (CD4) and virologic (HIV viral load) response to ART. 37/94 (39%) of HCV/HIV coinfected vs 10/94 (11%) with HIV had >2 fold increase in ALT, leading to medication substitutions in 8 patients and cessation of ART in 2 HIV/HCV patients compared to no substitutions or discontinuations in the group with HIV monoinfection. The authors reported hepatoxicity was seen at all time points in coinfected patients, although I m unsure how they defined hepatotoxicity.

A group from Jacksonville, FL. reported on the impact of HAART on HCV disease in HCV/HIV coinfected patients (Abhijit Roychowdhury, Div of GI, Univ of Florida Health Science Ctr, Jacksonville, FL, DDW May 2001). They compared histologic progression by biopsy in HCV/HIV coinfected patients who received HAART to a group that did not receive any medication. The authors concluded that HAART may play a role in slowing HCV disease progression as the French research group found. However, these authors did not analyze their results taking into consideration various covariables as the Sterling group did. The HAI inflammatory activity score in the HIV/HCV coinfected patients who received HAART was slightly less than the patients who did not without HAART. They also reported HCV RNA level and HAI inflammation activity scores were slightly decreased in HIV/HCV patients on HAART, but there was no difference in HAI fibrosis scores when compared with the control HIV/HCV and HCV patients, suggesting that HAART may play a role in slowing HCV disease progression. They also reported that after being on HAART for 2 years or more, ALT (hepatoxicity) was more likely to increase.

Management of HCV Infection

Assessment of disease severity

In HIV-infected individuals, quantitation of the amount of HIV-1 RNA in plasma is both an important predictor of disease progression and a measurement of the efficacy of antiretroviral therapy. Additionally, the peripheral blood CD4+ T cell count provides important information concerning the severity of the disease. In HCV, several indicators can be used to assess the degree of disease severity: biochemical measurements (serum quantitation of alanine aminotransferase, ALT), virologic measurements (measurement of HCV RNA), and histologic measurements (degree of fibrosis and inflammation on liver biopsy). Unfortunately, symptoms do not usually present in chronic HCV infection until the development of end stage liver disease. These symptoms (ascites, encephalopathy, prolonged prothrombin time, elevated bilirubin, decreased serum albumin) comprise the Childs-Pugh scoring system, the most frequently used measure to assess damage in end stage liver disease.

Role of Liver Biopsy in Hepatitis C

The liver biopsy is the most specific test for the diagnosis and assessment of hepatic pathology. The first liver biopsy was performed in 1883 and the technique became widely used as a diagnostic method for liver disease in the late-1950s. Liver biopsies can be performed through the abdominal wall (percutaneous), through the jugular vein (transjugular), or through a laparoscope (laparoscopic liver biopsy).

The biopsy specimen represents 1/50,000 of the total mass of the liver, which is usually sufficient for the assessment of diffuse hepatic disease. In the management of chronic hepatitis C, the assessment of hepatic pathology can provide important information regarding the prognosis and management of the infection. In HCV, the amount of hepatic fibrosis, as opposed to the level of HCV RNA, is the most important prognostic factor.

Currently, the only method by which to quantitate the amount of hepatic fibrosis is through a liver biopsy, which should be performed in any HCV-infected individual being considered for treatment. The biopsy is graded for the amount of inflammation and the stage of fibrosis on a 0 to 4 scale. Treatment should be more aggressively pursued in a patient who has stage 2-3+ fibrosis in the liver. Additionally, there is a poor correlation between the aminotransferase level (ALT) and hepatic histological features that may result from HCV. A subgroup of HCV infected individuals may have normal aminotransferase levels with clinically significant fibrosis or cirrhosis. Therefore, most hepatologists recommend a liver biopsy for histologic assessment of the liver regardless of the aminotransferase or HCV RNA levels.

Although very rare, intraperitoneal hemorrhage is the most serious complication of a percutaneous liver biopsy usually occurring within the first two to three hours after the procedure. Ultrasound can be routinely used immediately before the biopsy to localize the site and after the biopsy to make sure that there is no evidence of postprocedure hemorrhage. If hemorrhage is suspected, arrangements for blood, platelet, and plasma transfusions are made. The interventional radiologists and the surgeons should be alerted that angiography or intraabdominal surgery may be necessary. In most cases, post-procedure hemorrhage can be managed conservatively.

Liver biopsies are usually performed on an outpatient basis provided that: 1) a reliable individual is able to escort the patient home and is able to stay with the patient overnight after the biopsy, 2) the biopsy was performed in a facility with an approved laboratory, a blood-banking unit, and an inpatient unit. Patients who have a liver biopsy should be monitored for 4-6 hours after the procedure. Ultrasonography, may also reduce the risk of complications from the liver biopsy by identifying clinically silent mass lesions and can define the hepatic anatomy relative to the gall bladder, lungs and kidneys.

In the event of contraindications to a percutaneous liver biopsy (i.e. uncooperative patient, history of unexplained bleeding, tendency to bleed [prothrombin time > 3-5 sec more than control, platelet count <50,000/mm3, prolonged bleeding time (> 10 min), or use of nonsteroidal antiinflammatory drug within previous 7-10 days], suspected hepatic hemangioma or echinococcal cyst), the biopsy can be obtained through the transjugular approach. Liver biopsies can also be performed via the laparoscope, although the frequency with which this procedure is performed has decreased in recent years.

Treatment of HCV

Goals of Therapy

The primary therapeutic goal is to eradicate HCV infection and in the process to effectively use predictors of a sustained therapeutic response. Other goals are to decrease the infectious pool, to achieve histologic benefit, and ultimately to improve quality of life. With current therapies, there are still a sizable number of patients with chronic HCV who do not respond to interferon and ribavirin therapy. However, even in patients who fail to respond to antiviral therapy, pegylated interferon might improve liver histology, slow disease progression and reduce the risk of hepatocellular carcinoma. Interferon is known to have an anti-inflammatory and an anti-fibrotic effect and the histologic benefit is most impressive in virologic responders and less so in viral nonresponders.

What is sustained virologic response (SVR)?

The same measurements that are used to determine disease severity (ALT, HCV RNA, and histological appearance on liver biopsy) are also used to determine if a therapeutic response has been achieved. Treatment for HCV is generally 48 weeks, or perhaps 24 weeks. In HIV/HCV coinfected individuals, 48 weeks of treatment is likely going to be the standard of care. The percent of patients with undetectable virus (<100 copies/ml) when treatment is stopped is called the End-Of-Treatment (ETR) Response. The key evaluation of therapy is the SVR. The SVR is the percent of patients with <100 copies/ml 24 weeks after treatment is stopped. The reason the SVR is the more important evaluation of the success of therapy is because patients who achieve an SVR are more likely to retain undetectable viral loads for years. Several small studies show that well over 90% of patients who achieve an SVR still have undetectable HCV for as long as they have been followed so far which is as far as 11 years. Some patients who achieve only an ETR can experience a viral relapse before 6 months after stopping therapy. So, the primary goal of therapy is to achieve the SVR.

Factors that predict a successful therapeutic response

Unlike HIV, it may be possible to eradicate HCV and the optimal duration of therapy has become an important issue. Five independent characteristics have been associated with a sustained virological response: genotype 2 or 3, baseline viral load less than 3.5 million copies/mL, no or minimal portal fibrosis, female gender, and age less than 40. Recently, Poynard et al (2000) suggested that all HCV-infected individuals be treated for 24 weeks at which time HCV RNA should be determined by PCR. If HCV RNA is detectable, treatment can be stopped. If the PCR is negative and the patient has fewer than four favorable fac-

tors, treatment should be continued for an additional 24 weeks. Additional factors, such as medication adherence and dosing antiviral medication based upon an individuals weight, are discussed below.

How is HCV treated?

Initially, interferon monotherapy (three million units three times per week) was used for the treatment of HCV. In 1998, two multicenter randomized trials demonstrated that the combination of interferon alfa-2b plus ribavirin was more effective than interferon monotherapy in the treatment of previously untreated (na ve) patients with chronic hepatitis C. Recently, interferon has been conjugated to polyethylene glycol, which results in once a week dosing. Interferon monotherapy studies yielded sustained viral responses in 10-15% of patients. The 2 large multicenter randomized trials of interferon alfa-2b plus ribivarin showed improved sustained viral responses of 38%-41%. Initial study results of pegylated interferon plus ribavirin show about 54% sustained virologic responses with 48 weeks therapy. Virologic response varies by genotype and these results are discussed below.

At DDW (May 2001), Thomas Shaw-Stieffell (University of Rochester) discussed the **pharmacology of interferon**. Standard interferon alfa given 3 times a week has limitations. It is rapidly absorbed after an injection, is widely distributed throughout the body, and is rapidly cleared by the kidneys, leading to a short plasma half-life of around 6 hours. When it is administered three times weekly, serum interferon levels fluctuate with an undetectable level in between the days of administration.

HCV has a half-life of around 3 hours and with a daily production of approximately 12 billion virions. Therefore, the large swings in standard interferon alfa concentrations may lead to a lack of sustained pressure on the virus leading to viral persistance. Lack of sustained pressure may lead to genetic mutations that could confer resistance to the medications that are used to treat HCV leading to viral persistence. The concept of pegylated interferon addresses these concerns.

Being able to administer interferon less frequently with sustained concentration over time with very little peak to trough variation ought to provide more optimal therapy. This has led to the pegylation of interferon. Pegylated interferon is a process that attaches a polyethylene glycol (PEG) molecule to a compound (drug) to increase its circulating time in the body. The size of the PEG, its branched versus linear structure, and the permanent bond between the PEG and the interferon have resulted in a once-weekly medication that has sustained absorption and reduced clearance, which allows the interferon to remain active in the body attacking the virus over a full week. Currently, there are two formulations of pegylated-interferon in clinical study: Pegasys (peginterferon alfa-2a) that has a larger PEG molecule (40kDa) attached to interferon, and PEG-Intron (peginterferon alfa-2b) that has a smaller molecule of PEG (12 kDa) attached to the protein.

The size of the PEG and other characteristics of pegylation influence the absorption, distribution, biologic activity, and also the ultimate degradation and elimination of interferon. The ability of the native protein to produce an immunologic response may be favorably altered by pegylation. PEG can be linked to interferon alfa by various amino acid residues and can be a linear or branched short chain or a long chain. All of these physical chemical properties may influence the response of the immune system to HCV and interferon and these differences may result in differences in the clinical response to therapy.

PEG-Intron has a linear monofunctional PEG molecule attached at several sites, and a PEG molecule combined to another adjacent interferon alpha. It is a lyophilized powder, stored at room temperature that needs to be reconstituted before each injection and the dosing is weight based (generally, 1.5 ug/kg weekly). It has an early peak after subcutaneous injection with an absorption half-life of 4.6 hours and a time to maximum concentration of 20 hours. The maximum concentration achieved is around 1 ng/ml with concentration tapering off and decreasing below 0 .5 ng/ml by 72 hours and continuing steadily with a decline thereafter.

Pegasys has a branched PEG chain of approximately 40,000 daltons, yet it maintains accessibility to the interferon alfa binding site, and has perhaps tighter binding. It is refrigerated, administered as a fixed dose (generally, 180 ug weekly), and is dispensed as a solution that can be injected without the need for reconstitution. Its half-life is greater than PEG-Intron at 50 hours with a time to maximum concentration of about 80 hours and sustained concentrations maintained for 168 hours or thereafter. Pegasys is not weight based dosed, but has been studied at a standard weekly dose.

Current Review of Pegylated Interferon Data

As stated above, the current **standard of care for treatment of chronic HCV** infection has been Rebetron: interferon alfa-2b (Intron A) given at a dose of 3 MU as a subcutaneous injection 3 times a week PLUS ribavirin (Rebetol) given orally at doses of 1,000-1,200 mg/day. Tolerability of taking this regimen has challenges, and SVR rates obtained with standard IFN/RBV are relatively poor, ranging from approximately 30% for genotype 1 patients after 48 weeks of therapy to 65% for genotypes 2 and 3 patients regardless of the duration of therapy (24 or 48 weeks). From a patient perspective, these response rates are suboptimal and tolerability is a concern, especially since adherence to the regimen is crucial to success. Clearly, better treatments are needed, particularly those that can be better tolerated and lead to a higher rate of SVR. The response rates seen in studies with pegylated interferon plus ribavirin are vastly improved: 76%-80% for genotypes 2/3, and 46% for genotype 1.

John McHutchison (Scripps Clinic, La Jolla, CA) reviewed at DDW 2001 the data on PegIntron monotherapy reported by Trepo at the EASL Spring 2000 Conference. In a study of 1200 patients, the End-Of -Treatment Response (ETR) was 41%, 6 months after stopping therapy the SVR (Sustained Virologic Response- SVR) was 23%. This compared to a 12% SVR in the control arm (standard IFN 3 MIU 3 times per week). The relapse rate was 39% and the discontinuation rate was 9-11%. Dose reduction rate was 15%. McHutchison concluded that PegIntron IFN monotherapy has similar side effects compared to standard IFN, double the SVR Sustained Virologic Response, a similar relapse rate as standard IFN, and most genotypes 1 do not respond (14% vs 49% for genotype 2).

At the same EASL Conference, Zuezem reported on 500 patients randomized to receive either Pegasys once weekly or an induction regimen of standard IFN 6 MIU 3 times per week for 12 weeks followed by the standard dosing of 3 MIU 3 times per week. Both studies were 48 weeks of treatment followed by a 24-week follow-up period to evaluate SVR. The Pegasys ETR was 69%, the SVR was 38%. In the control arm the SVR was 19%, also double the response rate observed in the control group. Genotype 1 SVR was 28% vs 64% for genotype 2. Patients with HCV viral load over 2 million did not respond as well as patients with viral <2 million (52% vs 27%). The discontinuation rate was 7%. Dose reduction was reported as 8% for adverse events, and 14% for lab abnormality in Peg arm and 9% in induction arm--mostly due to neutropenia (decreased neutrophils)- it was 11% in Peg arm and 7% in other arm.

The PegIntron montherapy study (23% SVR) described above is the only PegIntron monotherapy study reported. Several Pegasys monotherapy studies have been reported at conferences showing response rates ranging from 30% to 38%.

Comparing the two formulations of pegylated interferons

Pegasys- There has been only one study for each of the Peg IFNs in combination with RBV. There has not been a head to head comparison of the two formulations of pegylated interferon, and it is difficult to compare them across studies in which patient populations are different and control arms are different. In the study reported by Michael Fried (University of North Carolina) at DDW Spring 2001, approximately 1200 Patients received 1 of 3 treatment regimens:

1. Pegasys 180ug once weekly by subcutaneous injection plus Ribavirin 1000-1200 mg per day
2. Pegasys plus placebo
3. Standard interferon a-2b 3 MIU (Million International Units) 3 times per week plus Ribavirin 1000-1200 mg per day

Biopsy was performed before and after therapy and the results are being analyzed and will be reported in the near future. Patient characteristics at baseline were: average age 42; male 68-73%; weight approximately 78 kg in all 3 arms, 64-66% genotype 1; HCV viral load about 6 million in all 3 arms; cirrhosis 15% in Peg monotherapy arm and 12% in other 2 arms.

The Pegasys+RBV sustained virologic response (ITT analysis) was 56% (n=453) overall compared to 45% (n=444) for standard IFN/RBV and 30% (n=224) for Pegasys monotherapy). Genotype 1 SVR was 46% vs 76% for genotype 2/3. Cirrhotic patients had 43% SVR in Pegasys/RBV arm compared to 33% receiving IFN/RBV. For patients without cirrhosis SVR was 58% for those taking Pegasys/RBVcompared to 47% for those taking IFN/RBV. Fried said that any patient receiving at least one dose of study drug was included in the analysis (Intent-To-Treat). See the discussion below on ribavirin dosing by weight.

Pegasys + RBV Intl Study Presented by Michael Fried at DDW

Pegasys	SVR
Pegasys/RBV	56%
IFN/RBV	45%
Pegasys monotherapy	30%
Peg/RBV Genotype 1	46%
IFN/RBV Genotype 1	37%
Peg mono Geno 1	21%
Peg/RBV Geno 2/3	76%
IFN/RBV Geno 2/3	61%
Peg mono Geno 2/3	45%
Cirrhotics (Peg/RBV)	43%
Cirrhotics (IFN/RBV)	33%

ITT (Intent-To-Treat) analysis used, which is more stringent than as-treated analysis.

To read full Pegasys report from EASL:
http://www.natap.org/2001/ddw/pegylated052301.htm

Peg-Intron- At the AASLD 2000 Conference, Michael Manns (Hannover Medical School, Hannover, Germany) reported week 72 results (48 weeks treatment followed by 24 week follow-up) for about 1500 treatment-na ve patients receiving 1 of 3 arms:

1. PegIntron (1.5 ug/kg once weekly for 4 weeks) plus Ribavirin 1000-1200 mg/daily and 0.5 PegIntron ug/kg for the next 44 weeks (n=514)
2. PegIntron (1.5 ug/kg once weekly for 48 weeks) plus Ribavirin 800 mg/daily (n=511)
3. Standard IFN (3 times per week) plus Ribavirin 1000-1200 mg/daily (n=505)

Biopsies were performed before and after treatment and evaluations are expected to be reported in future. Patient characteristics at baseline were: age 43, about the same in each group; about 67% men in each group; 90% Caucasians in each group; weight about 82 kg in each group. About 68% genotype 1 in all 3 groups; 67-69% had >2 million viral load; Manns reported cirrhosis 10% in each group at AASLD, but at EASL 2001 reported 40-44% had "bridging fibrosis or cirrhosis" (F3/F4) while the Schering printed literature said liver biopsy by local pathologist reported 28-30% (F3/F4).

PegIntron/RBV (full dose 1.5 ug/kg) combined with 800mg RBV showed an overall 54% SVR. Patients receiving standard IFN with 1000-1200mg RBV had a 47% SVR. 42% for genotype 1 vs 82% genotype 2/3 (ITT analysis). Patients with less advanced liver disease tend to respond better to treatment, so this should be a factor considered in deciding when to begin therapy. Manns reported that lower baseline fibrosis scores were associated higher SVR rates, a trend that has occurred in previous studies. When comparing patients with F1/F2 to F3/F4 fibrosis scores there was a difference in SVR of 5-7 percentage points.

PegIntron + RBV Study Presented by M Manns at EASL

PegIntron Study	SVR
PegIntron/ 800 mg RBV	54%, 52%*
IFN/RBV 1000/1200mg	47%, 46%*
Peg/RBV Genotype 1	42%, 41%*
IFN/RBV Genotype 1	33%
Peg/RBVGenotype 2/3	82%
IFN/RBV Genotype 2/3	79%
Peg/RBV Geno 1+hi viral load	30%*
IFN/RBV Geno 1+hi viral load	29%*

The data in the Table are an Intent-to-treat (ITT) analysis, which is a more stringent analysis rather than as-treated analysis.

* These data were reported in the recently issued (August 2001) FDA PegIntron/Ribavirin Label.

To read the full PegIntron reports from EASL:
http://www.natap.org/2001/36theasl/part4easl050101.htm
http://www.natap.org/2001/36theasl/part5easl050101.htm

Two studies find benefit in treating HCV during acute infection

There were two interesting poster abstracts at DDW 2001 addressing the unusual patient group--patients with acute HCV infection. They are unusual because they are hard to find. Therefore, treating this patient group has not been studied much. Just as in HIV its hard to identify patients with acute infection. It 's not until years later, in general, that patients get tested and find out they have HIV or HCV. In the Jaeckel study below, at the end of the 24-week treatment period, 97% of treated patients were virologic responders, whereas only 30% of untreated patients spontaneously cleared virus. I think that the sustained response at the end of the 24-week follow-up period in

the treated group was 70%. This was using the standard interferon without ribavirin, so using pegylated interferon with ribavirin ought to yield better results. Jaeckel suggests interferon monotherapy is adequate I suppose because of the high response rates he saw. In the Chone study (n=14), at the end of treatment 71% (n=10) were responders (HCV-RNA negative and normal liver enzymes). 60% of the responders had an average follow-up of 17 months & all were sustained responders. The studies concluded that treatment during acute infection can prevent chronic infection in a high percentage of patients and unexpected side effects do not appear to occur.

Suggested dosing of ribavirin by weight

It was reported at AASLD (November 2000) from the PegIntron/RBV study that dosing ribavirin by weight may improve response to therapy, but these data had limitations and are controversial. Study investigators did a retrospective analysis to see how much RBV concentration patients were receiving based on their body weights. To be clear, study patients were not randomized to receive different doses of RBV, as everyone received 800 mg per day of ribavirin. In the AASLD reported study, the authors reported patients with higher concentrations of RBV had better virologic responses: patients who had <65 kg weight at baseline had a 62% SVR; patients with 65-85 kg at baseline had a 55% SVR; patients with >85 kg had a 49% SVR. But, Manns concluded weight adjusted dosing of ribavirin with peginterferon alfa 2b will be confirmed in prospective studies. Two reasons for the controversy regarding the findings reported at AASLD is that patients with lower weight tend to respond better to therapy and that all patients in this study received the same RBV dose of 800 mg at baseline. Schering is now conducting a large prospective study to address this question in which patients are receiving different RBV dosing based on weight.

Based on their study conclusions, Schering recommends the optimum Ribivarin dosing with Peg IFN a-2b 1.5 ug/kg (10.6 mg per kilogram):

<65 kg in weight ribivarin dose should be 800 mg/day
65-85 kg = 1000 mg/day
>85 kg = 1200 mg/day

European authorities approved PegIntron with weight based dosing of ribavirin. The FDA has not approved weight based dosing of ribavirin. In their recent approval of ribavirin being sold unbundled from interferon, the FDA approved ribavirin dosing only with 800 mg per day in combination with PegIntron. Pegasys studies have not yet analyzed or explored response by weight based dosing of RBV, but studies are expected to be exploring this. Data should be forthcoming soon.

Adherence is crucial to HCV treatment success; apparently more so in genotype 1

We are very aware of the importance of adherence in HIV. Study results suggest that taking less than 95% of HIV medications can impact on reaching full virologic suppression. Adherence to HCV treatment is just as important and it has been evaluated by several investigators. Fried reported compliance with treatment at week 12 is associated with the highest probability of achieving an SVR. Of the 86% responders at week 12, 75% (n=184) achieved SVR when adherence was >80%. While only 48% (n=69) with <80% adherence achieved a SVR.

At DDW (May 2001), John McHutchison discussed how adherence impacted response in the PegIntron+RBV study. Patients who received PegIntron 1.5 + RBV 800 had a 54% overall SVR, but patients with >80% adherence had a 63% SVR while patients with <80% adherence had a 52% SVR. In referring to data using the standard interferon + RBV, adherence also mattered: 41% had a SVR, but when compared to patients with >80% adherence 48% had a SVR, and compared to patients with <80% adherence only 29% had an SVR.

McHutchison reported that 63% of patients in the study were adherent as measured by taking 80% of the medications 80% of the time for 80% of the study length. Men were more likely to be adherent than women (67% vs 53%). As would be expected, the overall SVR rate was higher among patients who adhered to the "80/80/80" criteria, except for patients in arm 2 (PEG 1.5) with genotypes 2 or 3, for whom there were no significant differences when comparing adherent to specified, partially non-adherent patients. This finding is most likely secondary to the very high SVR in genotype 2/3 patients. For patients with all genotypes in arm 2 (PEG 1.5), those who were adherent 80% of the time had a significantly higher SVR rate of 63% ("as-treated" analysis), compared to partially, non-adherent patients (52%, as-treated analysis) and the 54% rate in the ITT ("intent-to-treat") analysis. When considering only genotype 1 patients in arm 2, "80% adherent" patients had a significantly higher SVR rate of 51% (as-treated), compared to 34% of partially, non-adherent patients (as-treated) and the 42% rate in the ITT analysis. When considering only patients with genotypes 2 or 3 in arm 2, "80% adherent" patients had a similar SVR rate of 90% (as-treated) as partially, non-adherent patients (89%, as-treated), compared to 82% in the ITT analysis.

Predictability Analysis: Initial viral load response may predict final viral response

Besides adherence, the HCV decline slope during the first few months after therapy initiation may predict which individuals are likely to achieve an SVR. From the Pegasys+RBV study reported at DDW 2001, Fried reported an analysis showing that the initial viral load response seen in the first few months after starting therapy as well as patient adherence appear to be key factors in achieving sustained virologic response. Two-thirds of patients with a 2 log drop or undetectable PCR at week 12 went on to achieve an SVR 24 weeks after stopping 48 weeks of therapy.

At week 12 (n=453), 86% (n=390) had a 2 log drop in HCV-RNA and 14% did not (n=63). Of these 14% only 2 (3%) went on to have a SVR 24 weeks after stopping treatment. Thus, Fried concluded that there is a 97% predictive value that if a patient does not have 2 log drop or negative PCR by week 12 they will not reach SVR. Of the 86% with the viral response, 65% (n=253) went on to SVR and 35% (n=137) did not.

Adverse Events, Safety, Tolerability and Quality of Life

Following is a review of results from studies so far conducted. Still remaining to be seen is more widespread and long-term experience and observation from clinical use by doctors and patients. The rate of withdrawal due to symptomatic adverse events was 9.4% for standard IFN/RBV and 6.9% for Pegasys/RBV. Withdrawal due to a laboratory abnormality was 0.9% for IFN/RBV vs 2.6% for Pegasys/RBV. Neutropenia was the most common laboratory abnormality leading to withdrawal, which occurred in 3 patients. Neutropenia is a reduction in neutrophils, which are an important type of white blood cell.

At the 2000 November AASLD, results were reported from the PegIntron/RBV study on safety and adverse events by John McHutchison. However, the presentation was limited to those patients

in arms 2 and 3 whose baseline body weights led to ribavirin concentrations that were greater than 10.6 mg per kilogram.

For the patients in the upper concentration range of ribavirin (greater than 10.6 mg/kg), adverse events that occurred with a rate that was at least 10% higher in the peginterferon 1.5 g/kg arm (PEG) than in the standard interferon arm (IFN) were as follows: fever (46% in PEG versus 33% in IFN), nausea (43% PEG vs. 33% IFN); weight loss (30% vs. 20%); hair loss (45% vs. 32%); weakness (asthenia, 28% vs. 18%); and skin reaction at injection site (58% vs. 36%). Other adverse events that occurred in at least 10% of both treatment arms included: malaise, fatigue, headache, chills, "flu"-like symptoms, sweating, loss of appetite, diarrhea, vomiting, muscle and bone pains, joint aches, muscle aches (myalgias), anxiety, concentration ("thinking") problems, depression, insomnia (difficulty sleeping), irritability, coughing, shortness of breath, itchy skin, rash, and dry skin.

The following additional adverse events profiles have been reported. Nearly all patients experience one or more adverse events. In many but not all cases, adverse events resolved after dose reduction or discontinuation of therapy. Some patients experienced ongoing or new serious adverse events during the 6-month follow-up period. In the PegIntron monotherapy study comparing PegIntron 1.5 ug/kg (n=304) to Intron A 3 MIU 3x/week (standard IFN given 3 times per week; n=307), some key adverse events rates reported were: headache (64% vs 58%), fatigue (45% vs 50%), flu-like symptoms (25% vs 19%), rigors (43% vs 33%), fever (40% vs 30%), nausea (25% vs 20%), diarrhea (20% vs 16%), abdominal pain (13% vs 11%), neutropenia (6% vs 2%), thrombocytopenia -reduced platelet counts- (7% vs <1%), myalgia- (61% vs 53%), arthralgia (31% vs 27%), anxiety/irritability/emotional lability (28% vs 34%), alopecia -hair loss- (22% vs 22%), dry skin (11% vs 9%), rash (6% vs 7%), depression (27% vs 25%), insomnia (20% vs 23%), hypothyroidism (5% vs 3%), weight decrease (21% vs 13%), injection site inflammation (40% vs 16%).

In the study comparing PegIntron 1.5 ug/kg+RBV (n=511) to Intron A/RBV (n=505), common adverse events reported in the PEG-Intron/RBV group included myalgia (56%), arthralgia (34%) nausea (43%), anorexia (32%), weight loss (29%), alopecia (36%), and pruritus--severe itching- (29%). In the PEG- Intron/RBV combination therapy trial the incidence of severe adverse events was 23% in the INTRON A/RBV group and 31-34% in the PEG-Intron/RBV groups. The incidence of life-threatening adverse events was < 1% across all groups in the monotherapy and combination therapy trials. The most common adverse events were psychiatric which occurred among 77% of patients and included most commonly depression, irritability, and insomnia, each reported by approximately 30-40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all patients during treatment or during follow-up after treatment cessation. Incidence rates for other selected common adverse events comparing the PegIntron/RBV arm with the Intron A/RBV arm included: fatigue (66% vs 63%); weight decrease (29% vs 20%); concentration impaired (17% vs 21%); agitation (8% vs 5%); rash (24% vs 23%); dry skin (24% vs 23%). By the end of the 6-month follow-up period the incidence of ongoing adverse events by body class in the PEG-INTRON 1.5/RBV group was 33% (psychiatric irritability, insomnia, anxiety, etc), 20% (musculoskeletal--myalgia, arthralgia), and 10% (for endocrine and for GI). In approximately 10-15% of patients weight loss, fatigue and headache had not resolved.

Severe potentially life- threatening neutropenia (<0.5 x 10 9 /L) occurred in 1% of patients treated with PEG-Intron monotherapy, 2% of patients treated with INTRON A/RBV and in 4% of patients treated with PEG-Intron/RBV. Intron A is the brand name for standard interferon from Schering. Two percent of patients receiving PEG-Intron monotherapy and 18% of patients receiving PEG-Intron /RBVrequired modification of interferon dosage. Few patients (< 1%) required permanent discontinuation of treatment. Decreases in neutrophil counts were seen in 85% receiving combination PegIntron/RBV and in 60% receiving standard IFN/RBV. Severe depression in platelet counts (<50,000) occurred in 1% of patients taking PegIntron. The incidence and severity of neutropenia & thrombocytopenia were greater in the PegIntron group compared to the Intron A group. Neutrophil and platelet counts were decreased in 70% and 20% of patients (compared to 6% for those receiving Intron A/RBV), respectively, but generally return to pretreatment levels within 4 weeks after stopping therapy. Patients may require discontinuation or dose modification as a result of platelet decreases. In the PEG-Intron/RBVcombination therapy trial 1% or 3% of patients required dose modification of INTRON A or PEG-Intron respectively. Platelet counts generally returned to pretreatment levels within 4 weeks of the cessation of therapy.

In an analysis that included only patients in the upper ribavirin concentration range, study discontinuation due to adverse events occurred among 14% of PegIntron/RBV patients and among 13% of Intron A/RBV patients. The total discontinuation rates due to any reason were not presented. The discontinuation rate was 20% in the registrational IFN/RBV study, and its been suggested that the reduced discontinuation rates in the PegIntron/RBV study is due to better patient/side effect management. Dose modification was 34% in IFN/RBV arm and 49% in the Peg/RBV arm compared to 10-25% in the registrational 48 week IFN/RBV study.

Discontinuation for anemia was 0.8% in the full dose 1.5 ug/kg PegIntron/RBV arm compared to 0.2% in the IFN/RBV arm. Anemia (decrease of hemoglobin to less than 10 grams per deciliter) occurred among 14% of those taking PEG 1.5 mg/kg compared to 12% of those taking IFN. However, dose reduction due to anemia took place among the opposite percentages: 12% of those taking PEG, compared to 14% of those taking IFN. Yet, discontinuation due to anemia occurred only among 2% of PEG patients and 0.2% of IFN patients. Anemia associated with ribavirin may result in a worsening of cardiac disease. High-fat meals increase ribavirin blood levels.

Neutropenia occurred more often in the full dose 1.5 mg/kg Peg/RBV arm (grade 3- 18% vs 7%; grade 4- 2% vs 4%). Neutropenia (low white cell count) led to a dose reduction in 21% of PEG patients, but in only 8% of IFN patients. Discontinuation due to neutropenia occurred in identical percentages as discontinuation due to anemia (2% in PEG, 0.2% in IFN). Serious psychiatric events were similar in the two treatment arms: suicide (none); suicide attempts (one patient in PEG 1.5 mg/kg arm, none in IFN arm); and suicidal ideation (suicide thoughts, 6 patients in PEG 1.5 mg/kg arm versus 7 in IFN arm). Discontinuation due to psychiatric events occurred among 6% of patients who received PEG 1.5 mg/kg and among 4% of the patients who received IFN. The overall modification rate of drug dosing (among patients in the upper ribavirin range) was 49% among PEG/RBV patients (42% receiving PegIntron 1.5 ug/kg/RBV) and 34% among IFN/RBV patients.

When evaluating adverse events, there were fewer in the Pegasys/RBV arm than in the standard IFN/RBV arm in certain categories in the study presented by Michael Fried at DDW: myalgia 42% vs 50%, rigors 24% vs 35%, pyrexia 43% vs 56%, depression 21% vs 30%. For other adverse events the incidence reported was approximately equal in each group. We await further data from this study.

At DDW, Robert Perrillo reported from a study of 412 treatment-na ve patients receiving Pegasys or standard IFN a-2b+RBV (1000/1200mg/day). 25% had cirrhosis (Knodell fibrosis score of 3 or 4). 84% were Caucasian, 73% genotype 1, 40% <10(6) IU/mL viral load, ALT was 110-112. At week 24 about 56% in both arms had negative PCR.

Incidence of Most Common Side Effects (Pegasys vs IFNa-2b+RBV)

	Pegasys	IFN/RBV
Fatigue	66%	68%
Headache	56%	62%
Rigors	**45%**	**56%**
Nausea	**34%**	**46%**
Insomnia	**32%**	**42%**
Myalgia (aches)	31%	40%
Pyrexia (fever)	30%	38%
Anemia	2%	32%
Arthralgia	25%	24%
Depression	17%	23%
Prutitus (itching)	7%	20%

At week 12, patients receiving Pegasys (compared to patients receiving IFN/RBV) reported significantly less problems performing physical activities, better overall assessment of health & well-being, less reduced quality of life due to mental health and well-being, less distress over health and better positive well-being scores. Pegasys patients also reported better work productivity and less activity impairment: overall work impairment due to health, less activity impairment due to health, and less impairment while working due to health. Patients on Pegasys reported less weekly wages lost, less patients went from employed to unemployed (7% vs 18%). These data report improved safety and quality of life for Pegasys monotherapy over the first 12 weeks of therapy. Longer follow-up data is awaited. As well, post treatment data can be helpful.

Tolerability may be more important to HCV/HIV coinfected patients for many reasons including: having to simultaneously take HIV HAART therapy; anemia in the setting of HIV may be more of a problem; adherence challenges may increase as coinfected patients will be taking more medications; coinfected patients may have lower threshold for tolerability and may be dealing with more issues.

PegIntron tolerability data was reported at AASLD 2000. Ray Chung reported for NATAP: Abstract #590 found that health related quality of life measures were significantly better using the 0.5 ug/kg/wk PegIntron dose compared with conventional INTRON (standard interferon). Quality of life scores were comparable between PEG 1.0 and slightly worse with 1.5. The second abstract (#591) examined PEG-IFN-a-2a (Pegasys) given at a dose of 180 ug/wk for 48 weeks compared with the conventional Roferon regimen of 12 weeks of 6 MU tiw followed by 36 weeks of 3 MU tiw. Fatigue and quality of life indices were significantly better for Pegasys at weeks 2 and 12. These differences were seen at week 72 (24 weeks after stopping therapy), but were not statistically different. These data suggest that the side effect profile in the early going of therapy, usually the most difficult period of patients, will be better-tolerated. We await further long-term data regarding the efficacy of pegylated interferons with RBV in terms of tolerability.

Again, there are no direct comparisons of the two PEGs in a study and the data we have on tolerability is preliminary. After using these drugs in the clinic, experience will reveal more about the tolerability and quality of life both on therapy and following treatment.

Achieving SVR Improves Fatigue, Quality of Life, General Well-Being & Functioning

David Bernstein (North Shore Univ Hosp, Manhasset, NY) reported at DDW on a pooled analysis of 1400 patients from 3 large international studies that compared 3 Pegasys doses (90, ug, 135 ug, and 180 ug) with standard IFN a-2a (given either at one of two doses three times per week: 6 MIU for 12 weeks followed by 3 MIU for 36 weeks or 3 MIU for 48 weeks). Patients were monitored for 24 weeks after stopping therapy. In all patients with sustained viral response (SVR) and in those patients with SVR without cirrhosis, significant improvements on both measures of fatigue and all SF-36 scores were seen. SF-36 Health Survey evaluates health related quality of life (physical functioning, body pain, general health, vitality, social functioning, emotional & general mental health), positive well-being, distress over health, and overall physical and mental health. Patients with SVR with cirrhosis showed significant improvement in these evaluations, but not quite as much as the others achieving an SVR. Bernstein also reported that the patient s responses to these evaluations of fatigue and other measures of well-being were predictive of patient discontinuation from treatment, suggesting that improved tolerability of treatment should help patients stay on therapy. Unfortunately, virologic nonresponders at week 72 reported worsened scores in fatigue and SF-36.

Affect of HCV on the Brain, Fatigue, Hostility, and Anger

Preliminary studies suggest that HCV can infect the brain just as in HIV. They also suggest that many people with HCV experience problems with fatigue, anger, hostility, and emotional distress. The affect of HCV on the brain may contribute to these other conditions. Coinfected patients may have a worse experience since viral and chronic diseases can contribute to this problem and both HIV and HCV can infect the brain. The presence of diabetes may also aggravate the condition.

Treatment of Adverse Events

Erythropoietin for interferon and ribavirin associated anemia

This initial pilot study suggests that EPO may be helpful in treating anemia for patients receiving HCV therapy (IFN/RBV). The study compared patients with reduced hemoglobin on IFN/RBV therapy receiving EPO vs standard of care management. Long-term adverse events data that could be related to EPO are not available since this is a pilot study. Preventing or treating anemia ought to improve a patient s ability to tolerate therapy, to adhere to therapy and to remain on therapy. Interferon+ribavirin can result in significantly reduced hemoglobin (anemia) in the first few weeks of therapy. Doug Dieterich (Cabrini Hospital, New York University Medical Center) reported data (DDW May 2001) from a study showing that Epoetin alfa (EPO) once weekly increased hemoglobin levels (mean change 2.9 g/dL vs 0.3 g/dL, P<.05) after they had fallen on HCV therapy from 14.5 to 11. Also, patients were able to maintain taking a higher dose (926 mg/day vs 782 mg/dayof ribavirin, p<.05) (lower hemoglobin can lead to reducing RBV dose), which may translate into a better virologic response. And the data suggested patients benefiting from EPO had less depression (which is a side effect of interferon and ribavirin therapy) and patients reported a better quality of life. This suggests that depression experienced on RBV/IFN may be due to at least in part to fatigue and anemia. Another study reviewed below shows less anemia was experienced by patients taking Pegasys alone (without ribavirin) compared to patients taking standard interferon with ribavirin.

At DDW, Mark Sulkowski reported that women are 4.4 times more likely than men (20% vs 4.5%) to experience a Hb <10 g/dL. Men were at a greater risk (40%) than women to experience a decrease in Hb of 3 or more g/dL from baseline. But men generally have higher Hg levels, and women menstruating also lose Hg every month. Sulkowski also reported that daily IFN therapy was not associated with a greater decline in Hb than IFN three times per week by week 4 of treatment. In a subset of anemic patients with a mean Hb of 10.7 g/dL who had RBV dose reduced to 600 mg daily, Hb levels increased by a mean 1.1 g/dL at 4-8 weeks after the dose decrease.

Sulkowski retrospectively analyzed treatment-related changes in Hb in about 600 participants in 2 studies (IFN na ve and experienced) randomized to receive RBV 1000 mg daily or 1000-1200 mg daily (based on weight) plus various daily or three times per week dosing regimens of IFN. More than 80% of women at baseline had Hb 13 g/dL or greater, and more than 90% of men had 14 or more g/dl Hb.

As expected, 10.3% (57/551) of patients had a Hb <10 g/dL. Hb decreased 3 or more g/dL in 54% of all patients. About 27% of men & women reached a nadir (lowest point) of 11-11.9 Hb, while many more men were able to maintain Hb 12-12.9 (25% vs 17%) and 13 or more (30% vs 10%). Sulkowski also reported that in a univariate analysis, increased age, higher baseling Hb and platelet counts, and CrCl (decreases in creatinine clearance) were significantly (P<0.5) associated with the largest Hb decreases.

The initial dose of EPO was 40,000 Units subcutaneously once weekly. Patients with an increase in Hb of 1 or more g/dl continued EPO. Patients with less than 1 increase stopped EPO. If Hb increased to >14 g/dL for women or 16 for men, EPO was withheld. When Hb subsequently decreased to 13 g/dL for women or <15 g/dl for men, EPO was resumed at 30,000 Units once weekly. I think Dieterich said he titrated (incrementally increased doses) by 5,000-10,000 to a maximum of 40,000 Units once weekly.

Primary endpoints were change in Hb, secondary endpoints were change in RBV dose, and change in quality of life measured by SF-12. At study entry there were 36 patients (24 men, 12 women) receiving EPO and 28 standard of care (20 men, 8 women). Age was 50 in EPO arm, and 48 in SOC arm. Weight (kg) was 88 in EPO arm, and 78 in SOC.

RESULTS:

The Hb values before RBV/IFN treatment was 14.5 (10.6-16.9 range) for the 36 patients receiving EPO, and 14.6 for the SOC arm (range 11.6-17.0), so it was about the same before treatment.

--Prior to week 16 there were 15 (42%) discontinuations in the EPO arm vs 14 (50%) in the SOC arm.

--At the start of receiving EPO the mean Hb levels were 11.0 in the EPO arm vs 11.0 in the SOC arm.

--At week 16 (ITT analysis), the mean Hb was 13.9* (+/- 1.7; range 10.4-17.2) in the EPO arm vs 11.3 (+/- 1.2; range 9.2-13.3) in the SOC arm, and the mean change in Hb was a 2.9 (+/- 1.8)* g/dL increase (range —0.3-6.9) for patients receiving EPO vs a 0.3 (+/- 1.0) mean increase in the SOC arm (range —1.3-2.5), (* EPO vs SOC p<.05). Kaplan-Meier plot evaluating measures over time (on-treatment analysis) showed both arms with 11 Hb at baseline and at week 16 Hb level was 14.2 (+/-1.7) g/dL for the EPO arm (n=21) vs 11.2 (+/- 1.3) g/dL in the SOC arm, n=14, (EPO vs SOC p<.05).

--By ITT analysis, 88% (30/34) in the EPO arm had 1 g/dL or more increase in Hb compared to 28% (8/28) in the SOC arm.

--Perhaps more important, RBV dose was higher in the EPO arm at week 16 (ITT) suggesting patients may be helped to tolerate adequate RBV dose by taking EPO. At study entry the mean RBV dose was 956 (+/- 242; range 200-1200) in the EPO arm vs 961 (+/- 175; range 600-1200) in the SOC arm. At week 16, the EPO arm dose 926 (+/- 234)* mg/day vs 782 (+/- 244) in the SOC arm. The mean change was —179 (+/- 203) in the SOC arm vs —31 (+/- 160)* in the EPO arm (EPO vs SOC P<.05). Using on-treatment analysis at week 16, the RBV dose was 900 (+/- 238) mg/day in the EPO arm (n=20) vs 707 (+/- 217) mg/day in the SOC arm (n=14), EPO vs SOC p<.05).

--By ITT analysis a higher percentage of patients receiving EPO (85%, 29/34) were able to take 800 mg or more RBV per day vs 61% (17/28) in the SOC arm. Only 15% receiving EPO were taking <800 mg/day vs 39% not receiving EPO (EPO vs SOC p<.05).

--A greater percentage of patients (56% vs 39%) were able to achieve a higher weight based RBV dosing (>10.6 mg/kg) in the EPO arm compared to the SOC arm, but this was not statistically significant. This 10.6 mg/kg level was suggested by Schering as the level of RBV dosing based on weight that patients should be above to achieve a maximum virologic response using PegIntron+RBV. This has been controversial as Roche suggests RBV weight based is not necessary for Pegasys+RBV, and Roche is collecting data now to report on this question. (See section on weight-based dosing, page 7.)

--In both the physical and mental components of the Quality of Life Test SF-12, the patients receiving EPO had better scores (ITT analysis) in both the physical and mental components than those not receiving EPO (physical component mean 4.5 [+/- 9.1; range 14.8-28.4] vs 1.5 [+/- 9.6; -20.4-26.9]; effect size between groups 0.38. Mental component mean 3.0 [+/- 9.7; range —21.6-25.4] vs 0.2 [+/- 6.9; range —12.9-23.6]; effect size between groups 0.25.

--In total, 29 patients were treated with 40,000 Units once weekly of EPO. 5 patients were dose reduced to 30,000, 20,000 or 10,000.

--Safety & tolerability: Dieterech reported EPO was well tolerated, that adverse events were similar to those expected with RBV/IFN, and adverse events were not significantly different across the study groups (including ALT & HCV-RNA). Dieterich reported no adverse events were significantly more frequent in the EPO group. He reported a final list of adverse events which patients experienced at greater than 20% in either group. For some adverse events the differences between the 2 groups was larger. He reported more patients had headaches in the EPO arm (26%, n=9 vs 11%, n=3), and nausea (23%, n=8 vs 7%, n=2), and pain (20%, n=7 vs 14%, n=4). Interestingly, only 17% (n=6) reported depression in the EPO arm compared to 32% (n=9) in the SOC arm suggesting that fatigue may be related to depression experienced on RBV/IFN. In other categories of adverse events there were no differences or smaller differences between the EPO and SOC arms: fatigue 29%, n=10 EPO vs 25%, n=7 SOC; alopecia 20%, n=7 vs 28%, n=8; dyspnea 20%, n=7 vs 25%, n=7; rash 20.6%, n=7 vs 17.9%, n=5; anorexia 11.8%, n=4 vs 21.4%, n=6.

Less Anemia with Pegasys Alone vs Standard IFN a-2b+Ribavirin

Kenneth Rothstein (Albert Einstein Medical Center, Philadelphia, PA.) reported on a safety, tolerability, efficacy, and quality of life study comparing Pegasys alone to standard IFN a-2b+ribivarin therapy. About 200 patients in each arm received either Pegasys (IFN a-2a) 180 ug once weekly or IFN a-2b 3 MIU three times per week plus RBV 1000-1200 mg/day. Preliminary virologic response at week 24 showed the same response (56% in Peg alone arm vs 57% in the IFN/RBV arm).

The incidence of adverse events were reported as less in the Pegasys arm: less rigors, nausea, insomnia, myalgia, pyrexia,

depression and pruritus (itching). Two percent were reported to experience anemia in the Pegasys arm vs 32% in the IFN/RBV arm. About 60% in the IFN/RBV arm vs 10% in the Pegasys arm had 10 or less g/dL Hb or a drop of 3 or more in Hb. 33% vs 2% (Peg vs IFN/RBV, respectively) had 10 g/dL or less Hb or a drop of 4 or more in Hb. There was also a wide disparity when looking at drops of 5 or 6 or more in Hb or 10 or less in Hb.

Patients reported better physical functioning scores, mental health, and better overall health & well-being at weeks 4 and 12 using Pegasys compared tostandrard IFN/RBV. Patients also reported better distress scores and positive well being scores. Patients also reported less work and activity impairment and impairment while working due to health when receiving Pegasys compared to RBV/IFN. Less patients taking Pegasys went from employed to unemployed at week 4 or 12 (7% vs 18%).

Other Issues in HCV Treatment

Improved Histology and Maintenance Therapy; Improved Liver Condition for Nonresponders

In individuals who have not achieved an SVR, interferon (or interferon in combination with ribavirin) may be continued for a prolonged period of time. Defined as "maintenance therapy", a prolonged course of interferon may improve hepatic histology, may delay progression of hepatic fibrosis, and may prevent the development of hepatocellular carcinoma. Interferon has an antifibrotic and antiproliferative benefit that is independent of its antiviral effect. This is the basis for maintenance therapy and data suggesting that interferon may slow or prevent progression to HCC.

From an analysis of multiple studies of Pegasys, the histologic response, as defined by an improvement of least 2 points in the histologic activity index (HAI) overall, was found in 57 % of treated patients compared to 41% of patients receiving standard interferon. The histologic response was most evident in those patients with SVR, in whom 83% also achieved a histologic response. A histologic response was observed in 79% of the patients who received standard IFN. However, it is important to note that even the non-responders derived histologic benefit, with 47% having a histologic response compared to 30% receiving standard IFN. Histologic improvement has been observed in studies involving PEG-Intron. Using PegIntron 0.5 ug/kg dose Knodell HAI inflammation score decreased 5 points after 24 weeks post-treatment, using 1.0 ug/kg inflammation score was reduced 5.4 points, using highest dose of 1.5 ug/kg the HAI score was reduced 4 points, and using standard interferon the HAI score was reduced 4.7 points.

Several studies show improved histology can be achieved with or without virologic response and the studies suggest that this may slow disease progression, stop or slow progression to cirrhosis, and may help prevent liver cancer. These study findings have not been definitive but two four-year studies in HCV-infected patients started in 2000 to try to confirm these preliminary findings (HALT-C, Pegasys; COPILOT, PegIntron). However, for patients with advanced liver disease maintenance therapy may be the only option for slowing progression to cancer or severe complications of hepatitis C. The key may be to find a tolerable dose.

Data was discussed at DDW from several studies regarding the observation of potential benefit by interferon on histologic response. Mitch Shiffman s randomized pilot study (Gastroenterology 1999;117: 1164) demonstrated the effect of maintenance therapy. Patients who after 6 months of treatment had significant reductions in serum ALT level (62.6 – 9.6), HCV-RNA titer (4.79 – 0.13 copies/mL), and hepatic inflammation (4.0 – 0.2) had reduced inflammation and a trend toward decreased fibrosis in the group that completed 30 months of maintenance therapy compared to the group that completed 6 months (80% vs 43%). The improvements seen on therapy were maintained in the patients randomized to continue interferon. Stopping treatment was associated with an increase in serum ALT, HCV-RNA, and a return of hepatic inflammation back to baseline. After 30 months of treatment, mean fibrosis score declined from 2.5 to 1.7 and 80% of patients had histological improvement. Discontinuation of interferon was associated with an increase in the mean fibrosis score and worsening of hepatic histology in 30% of patients.

For patients with advanced HCV, the potential for slowing disease progression is very important. If a patient does not achieve an SVR from therapy, maintaining a lower dose of interferon therapy (maintenance therapy) may prevent or slow disease progression. And maintenance therapy may be the key to sustaining improved histology. Although the Shiffman study showed benefit for maintenance in patients who demonstrated significant improvements during the 6 months on therapy, it was a pilot study and did not look at potential benefit for patients who did not demonstrate such clear benefit from initial therapy. It s possible that maintenance therapy may sustain much less of a benefit seen during the first 6 months of therapy, that is, small improvements in histology may be sustained.

ALT does not correlate with hepatic inflammation or fibrosis

The effect of a therapeutic response in individuals with normal ALT were presented by Juan Esteban in at AASLD 2000. Several hundred patients were followed for over 8 years and each had two liver biopsies separated by four years. A portion (about 150 patients) were treated with interferon or IFN+ribavirin. Although Esteban did not indicate it, I assume the patients were mono-HCV-infected and not coinfected. He compared those with normal ALT to those with abnormal ALT and found a higher percentage of females in the normal ALT (71%) compared to abnormal ALT (47%). Any alcohol intake was noted in 21% of those with normal ALT and in 40% of those with abnormal ALT. Heavy alcohol intake, defined as greater than 50g/day, occurred in 6% of those with normal ALT and in 17% of those with abnormal ALT. Hepatic histology as determined from liver biopsies differed between those with normal and abnormal ALT (biopsies were scored according to Ishak et al. and fibrosis progression rate per year estimated as the ratio between fibrosis score in the first biopsy and duration of infection [indirect estimate], and difference between fibrosis scores divided by the time interval between biopsies [direct estimate]).

Significant differences were seen in liver damage between those with normal and abnormal ALT. Perhaps most importantly observed in this study and also seen in several other studies, ALT does not necessarily predict the stage of liver disease. Moderate and more advanced liver disease can be present when ALT is normal. This may be a more crucial consideration in coinfection since liver disease progression can be accelerated by HIV. In those with normal ALT (biopsy performed), 55% were mild, 36% were moderate and 2% severe chronic hepatitis, and 2% cirrhosis. In those with abnormal ALT, 24-29% had mild biopsy results, 32-48% moderate, 19-27% severe chronic hepatitis, and 5-17% cirrhosis. Four years later, a repeat biopsy in individuals with normal ALT showed no cirrhosis, decompensation, hepatocellular carcinoma or death. In 114

patients with abnormal ALT, 8% had progressed to cirrhosis, 2% had decompensated liver disease, 2% had hepatocellular carcinoma and 2% had died.

Interestingly, Esteban's data in the program abstract indicated patients with elevated ALT saw increased fibrosis if untreated or if they were non-responders to HCV treatment, but decreased fibrosis in those with sustained viral response. However, it is not clear how Esteban defines nonresponders. Irregardless, some non-responders to IFN still had an improvement in hepatic histology (18%) or stopped fibrosis progression (49%). The proportion of patients whose fibrosis improved or remained unchanged was higher in non-responders than in untreated patients. Additionally in follow-up, non-responders treated with IFN+RBV saw their fibrosis progression rates decrease (from 0.215– 0 to 0.057– 0.350; p=0.02), while it remained unchanged in untreated patients and non-responders treated with IFN alone. Esteban concluded that combination treatment slows disease progression in virologic non-responders but that the duration of benefit remains unclear. This study supplies more evidence that maintenance therapy may be beneficial and it suggests that maintenance therapy including RBV maybe more beneficial than IFN alone. Esteban also suggests in his conclusions that ALT may help predict disease progression, but ALT is no substitute for a biopsy. More details on this study are available on the NATAP web site where the abstract will be available. NATAP AASLD 2000 Conference Report-

http://www.natap.org/2000/aasld/dal_rp11more_evidence.htm

Also available on the NATAP website:
"Maintenance interferon for chronic hepatitis C: More issues than answers?"
Written by Gregory T. Everson, M.D., presents an interesting overview.

http://www.natap.org/2001/apr/maintenance043001.htm

Liver transplants in coinfection & HCV recurrence following liver transplantation

Histologic recurrence develops in at least 50% of patients within the first year after transplant, with progression to cirrhosis in about 20%. High lipids and diabetes are negative risk factors. One of the challenges of transplantation is to prevent reinfection and particularly progressive liver disease following liver transplantation. Encouraging but preliminary data was presented on treating established recurrence with Pegasys 180 mg given weekly for 48 weeks. Preliminary week 24 data demonstrated that about 44% had a 2 log10 drop in HCV-RNA and 25% were HCV-RNA negative. In a separate study, Firpi reported at DDW that 20% receiving standard interferon with 1000-1200 mg daily ribavirin for 12-18 months had a sustained viral response (6 months after stopping therapy). Of the 50 patients who qualified for this study, 4 died, 3 required discontinuation, and 38% dose reduced.

HIV-infected patients are not generally prioritized for liver transplants. Reimbursement is an issue because insurers consider transplants in coinfected individuals to be experimental. In spite of the many advances in organ transplantation, the presence of HIV in a patient has been considered a contraindication to transplantation. The following summarizes the current concerns: (1) a stable HIV-positive candidate will immunologically decompensate with immunosuppression (from immunosuppressive drug therapy used following transplant); (2) the viral load will increase and/or immunosuppression may enhance HIV mutations (patients go off HIV therapy briefly after the transplant); (3) the pharmacokinetics and pharmacointeractions of current antiretroviral agents and immunosuppression may lead to subtherapeutic effects or toxicity; and (4) the public perception of offering transplantation to HIV-positive patients will lead to diminished support for donation. With the use of HAART and the therapeutic successes that have resulted from its use, liver transplants in HIV have become more viable.

Several transplant sites throughout Western Europe and the US are performing liver transplants in HBV or HCV infected patients who are also infected with HIV. The University of Pittsburgh appears to have the best success rate and has been the most willing to transplant coinfected patients. They also appear to have a helpful reimbursement program. Their survival rates appear to be comparable to those of transplant patients without HIV.

Pittsburgh has done a total of 7 liver transplants and 4 kidney transplants in the HAART era. Previous information was that 1 patient had died relatively early (2 weeks after liver transplantation) due to poor graft function and requirement of life support prior to surgery. Since then, there has been 1 additional death at 20 months due to chronic rejection in a patient who became "noncompliant" when the protease inhibitor was discontinued without appropriate adjustment of tacrolimus levels (unbeknownst to the transplant team), with resultant rejection. The remaining 9 patients are all alive with stable HIV disease. Fung is publishing the results of the 7 liver patients with the 5 from Miami, Florida. None of their patients has died.

Effect of Diet on HCV

In general, good nutritional principles should be followed by all individuals, and even more so if they are infected with HCV. For the vast majority of HCV-infected individuals, no dietary modification is necessary. Individuals who have decompensated liver disease may need to restrict protein intake. Iron supplementation should only be undertaken after consultation with a physician. Iron absorption is very tightly controlled by the body and intake in most individuals is much more than is needed. The question remains whether we should be proactive about early dietary changes for persons infected with Hepatitis C but who have not manifested symptoms of liver failure? While an ounce of prevention is worth a pound of cure, changing eating habits is very difficult to make and harder to adhere to.

Recommending vitamin and herbal supplements can get expensive and may not significantly increase quality of life. This by no means implies that people with Hepatitis C should not pay attention to their dietary habits and nutritional requirements. Each individual will need to be evaluated by a dietitian with experience in liver disease to determine his or her own requirements. The reason for this is because people do not select their diets based on physical and/or medical requirements alone, but also from their cultural upbringing, access to food/meals, and certain habits set by choice and convenience.

A nutritional foundation of dietary practices should be the guide for persons with Hepatitis C, especially at times when there are no gastrointestinal symptoms and liver function tests are normal or mildly elevated with no other clinical abnormalities. Perspectives on diet and nutrition are offered below, including from Jocelyn Rodrigues, MPH, RD, CDN. A healthy balanced diet including reasonable amounts of red meat is desirable, unless otherwise indicated by a patient s condition:

1. Get half of your daily calories in carbohydrates. Whole grain starches, vegetables and fruits should be the mainstay of carbohydrates. Sugar and sugary foods, like donuts and candy bars, should be minimized. If you have diabetes, speak to your doctor.
2. Keep protein intake up. Have some protein at every meal. Portion matters more than kind of protein. Make sure to include beans and tofu products, nuts, and dairy products.

3. Moderate fat consumption. Cutting back sugary foods tends to reduce fat intake. Nuts and tofu, which are protein sources, have a healthy amount of unsaturated fat. Use vegetable oil and butter sparingly. The goal in reducing fat intake is mainly for weight purposes.

4. Maintain or achieve desirable body weight. Those who are obese, more than twenty pounds over their ideal weight for height, should lose weight. Those who are mildly overweight should watch out for insidious weight gain.

Marion Peters, MD, Hepatologist and GI specialist at UCSF says: if a patient has encepholopathy, which can occur as part of decompensated cirrhosis, they should limit their protein intake, but not necessarily eliminate red meat. Iron accumulation can be a problem only if you eat excessive amounts of red meat. Otherwise, eating red meat is fine and in fact could be part of your diet. Just don t eat red meat three times per day. If you are taking HCV therapy, you should indulge yourself a little to increase caloric intake and particularly it s ok to eat red meat. Dr Peters says that studies suggesting iron accumulation in the liver can be a problem is when iron intake is very high and excessive.

On the topic of iron storage in the liver and it s potential harm, Ms. Rodrigues says: from a nutrition perspective, the following is known--

1. Iron is poorly absorbed through the GI tract. Heme-iron (ie. meats) have a better absorption rate but absorption is not 100%. Non heme-iron (ie. fortified flour, cereals, spinach, etc) is better absorbed than meat, yet absorption still is not 100%. Therefore, at any given high iron meal a maximum of 40-50% of the iron is absorbed. Iron supplementation helps increase the likelihood for absorption.

2. During inflammation (ie. fever) iron storage in the liver is increased. Diabetics and certain substance abusers may have conditional hemochromatosis. (a hereditary disorder of iron metabolism characterized by excessive accumulation of iron in tissues, diabetes, liver dysfunction, and a bronze skin pigmentation).

3. As for HCV, earlier studies suggested that increased liver iron levels elicit liver oxidative stress, with consequent steatosis (fatty liver) and glutathione depletion. (Iron storage, lipid peroxidation and gluthathione turnover in chronic anti-HCV positive hepatitis. J. Hepatol 1995 Apr;22(4):44-56 , Therapy of hepatitis C: other options. Hepatology 1997 Sep;26 (Suppl 1): 143S - 151S.) Therefore, Rodrigues feels that this information suggests high iron levels may be harmful to the liver.

However, Ms Rodrigues says the question of whether to restrict or supplement iron intake needs to be considered individually, taking into consideration person's dietary habits, results of laboratory tests including testing of iron levels, medications, physical health, and medical history. It is safe to say, that for men with elevated iron levels (serum ferritin especially), taking a multivitamin without iron is recommended. Women who are premenopausal should consider iron supplementation, unless otherwise indicated, if serum ferritin is high and there is grade 2 or 3 fibrosis. But in post-menopause iron supplementation may not be suggested. Women who are experiencing heavy bleeding during menstruation may need iron supplementation. But these situations vary by individual and consultation with your doctor is recommended. Men and women who start interferon/ribavirin treatment will need to be reassessed. As liver inflammation subsides with IFN/Riba, serum ferritin will normalize, and depending on the person's dietary intake and total iron, iron supplementation may be indicated. Decreased serum ferritin is a sensitive indicator of iron deficiency, however it may not be reliable if there is co-existing inflammatory infection or co-existing liver disease such as Hep B or Hep C.

Treatment of HCV in Special Populations

Hard To Treat Populations: African-Americans, genotype 1 & 4, cirrhotics, nonresponders & relapsers

Hard to treat populations are also seeing improved response rates with pegylated interferon. In an analysis of African-American s response to standard interferon alfa-2b plus ribavirin in a large study conducted by Schering-Plough, John McHutchison has reported that African-Americans responded as well as Caucasians with genotype 1 (25% in Caucasians vs 22% in African-Americans). Some experts have questioned this equivalence and some studies have shown less response by African-Americans, while anecdotal reports have reported a decreased response to therapy by African-Americans. A large, NIH-funded study will address the reasons why African-Americans manifest decreased responsiveness to treatment of HCV. Some experts feel that there may be genetic differences in the immune response. It appears that adherence is just as important in taking HCV medications as it is in HIV. Cirrhotics saw a very nice 30% response rate to Pegasys monotherapy in a study that was reported by Heathcote in 2000. Preliminary data reported by Ira Jacobson (Cornell) at DDW in 2001 showed that 30% of previous non-responders to standard interferon plus ribavirin with genotype 1 were PCR negative at week 24 with pegylated interferon plus ribavirin therapy.

Study results using both pegylated interferons show African-Americans improve the response rate over use of standard interferon. Following PEG-Intron monotherapy treatment: 14% of African-Americans/Blacks had SVR and none who received standard interferon achieved any benefit. Analysis of data from the Pegasys monotherapy data base (55 African-American patients) noted that 15% of African-Americans/Blacks achieved SVR to this monotherapy as compared to 34% of Caucasians. None of the African-American patients who received standard interferon monotherapy had achieved SVR. In terms of ALT, 19% of African-Americans achieved normal ALT compared to 39% of Caucasians. Only 7% of African-Americans achieved normal ALT using standard IFN. In terms of a histologic response, 33% of African-Americans had a decrease of 2 points in HAI score compared to 61% for Caucasians, no doubt due to an improved SVR rate. Only 28% of African-Americans using standard IFN achieved a histologic response. In terms of hepatic fibrosis progression, several studies suggest that HCV disease may progress more slowly in HCV monoinfected patients compared to that in HIV/HCV coinfected patients. Study research also suggest HCV may progress more slowly in African-Americans with HCV alone, but this has not been studied in coinfected African-Americans, nor are we well acquainted with the clinical significance of this suggested slower progression.

Cirrhotic patients are also considered to be difficult to treat. Thirty percent of cirrhotic patients achieved a virologic response to Pegasys 180 ug given once a week for 48 weeks, which was comparable to the 35% response rates in non-cirrhotics. These data are encouraging for difficult to treat African-American/Black patients, cirrhotic patients, and those with genotypes 1 and 4. Traditionally, genotype 4 patients also have been difficult to treat, and relatively few individuals achieve SVR. Although quite infrequent, occasionally genotype 4 is encountered in the United States. In a subset analysis from the Pegasys database, 45% of genotype 4 patients achieved SVR. It was discussed earlier in this report how the response to pegylated interferon+ribavirin appears to have increased substantially for genotype 1, from the 29% seen in the large registrational study of IFN/RBV to 45% in the pegylated + ribavirin studies. Interestingly, the SVR for individuals with genotype 2

have not improved as dramatically in response to pegylated interferon and ribavirin as those in individuals with genotype 1 infection.

Pegylated Interferon + Ribavirin in Previous Nonresponders

Preliminary data from several studies presented at DDW and recently in other venues show promising results for patients who previously had viral failure from standard IFN+RBV, particularly for previous nonresponders. The first dataset comes from Ira Jacobson (Weill Medical College of Cornell University). Three groups of patients are being studied (n=330): IFN monotherapy nonresponders, combination relapsers, and combination nonresponders.

Patients receive a PegIntron+RBV regimen for 48 weeks: (group 1, n=68) PegIntron 1.0 ug/kg + RBV 1000 mg/day (if <75 kg) or 1200 mg/day (if >75 kg), or (group 2, n=57) PegIntron 1.5 ug/kg + RBV 800 mg/day. Therapy is discontinued if patients have detectable HCV RNA as determined by PCR at 24 weeks. At baseline, the average fibrosis stage was 1.8-1.9, ALTs were 93-104 IU/L, HCV RNA ranged from 1.1 x 10^6 to 1.6 x 10^6 copies/ml, genotype 1 was present in 81-91%. One hundred and twenty-three patients were reported to have reached week 24 of treatment.

Subjects who are treatment week 24 PCR Negative

	Grp 1 (n=68)	Grp 2 (n=55*)
Genotype 1	18/62 (29%)	19/46 (41%)
Geno non-1	4/6 (67%)	6/9 (66%)**
TOTAL	22/68 (32%)	25/55 (45%)

* 2 patients genotype pending
** 1 patient in group 1 & 2 patients in group 2 were genotype 4

IFN nonresponders	8/15 (53%)
IFN/RBV relapsers	18/18 (100%)
IFN/RBV nonresponders	22/90 (24%)
Genotype 1	18/81 (22%)
Genotype 2	4/9 (44%)

PCR Negative at week 24: treatment response to PEG IFN/RBV by Nonresponders (NR) and Relapsers.

	Grp 1 (n=68)	Grp 2 (n=55*)
Genotype 1 Combo-NR	8/48 (17%)	10/33 (30%)
Geno non-1 Combo-NR	2/4 (50%)	2/5 (40%)
Combo relapsers*	7/7 (100%)	11/11 (100%)
IFN monotherapy-NR	5/9 (56%)	3/6 (50%)

* 6 patients in grp 1 and 7 in grp 2 were genotype 1

In summary, Jacobson found that in genotype 1 nonresponders the 24 week treatment response is higher with 1.5 ug/kg of peg interferon (30% vs 17%). Preliminary results suggest very high response rates in combination therapy relapsers with either dose of PEG. In this group of patients, PEG IFN a-2b and RBV is associated with a similar side effect profile as combination therapy. No definitive conclusions can be reached until a larger number of patients have been studied and data on SVR become available.

Peg Intron/RBV for IFN or IFN/RBV Failures: 2 additional studies at DDW

Dr Gaglio (DDW) from New Orleans reported on 254 patients receiving Peg IFN a-2b 1.5 ug/kg + RBV 800 mg for 48 weeks in study for IFN or IFN/RBV failures. One hundred thirty two patients were treated for 24 weeks and virologic response (PCR negative) was seen in:

16/75 (21%) of nonresponders
9/17 (53%) in partial responders
22/29 (76%) in relapsers
6/8 (75%) in breakthrough relapsers

Dose reduction was required in about 20% of patients due to anemia (39%), leukopenia (35%), thrombocytopenia (19%), and dyspnea (6%). Medication discontinuation occurred in 3%. On the basis of these results, Dr. Gaglio concluded therapy was relatively well tolerated.

Peg IFN/RBV in IFN/RBV Failures

The second abstract included over 200 IFN/RBV nonresponders and relapsers from 11 midwest cities who were randomized to receive PEG IFN a-2b 0.5 ug/kg + RBV 800 mg/day or Peg IFN a-2b 1.5 ug/kg + RBV 800 mg/day. One hundred and two patients have completed 24 out of 48 weeks of therapy.

Of 66 nonresponders:

--3% (1/34) who received PegIntron 0.5 ug/kg+ RBV 800 mg are PCR negative.

--28% (9/32) who received 1.5 ug/kg + RBV 800 mg are PCR negative

Of 40 relapsers:

--52% (11/21) receiving lower dose IFN regimen are PCR negative

--68% (13/19) receiving PegIntron 1.5 ug/kg are PCR negative

Pegasys + RBV in IFN and IFN/RBV Failures

Preliminary data was reported (AASLD, June 2001) from the HALT-C study (which is a four year maintenance therapy study) by Adrian Di Bisceglie. At week 20, 40% (59/146) of patients who had previously not responded to interferon or IFN-ribavirin had negative HCV RNA. At DDW, Nezam Afdhal presented data from a small study that previous non-responders to combination therapy could respond well to Pegasys: HCV RNA is negative at week 24 in 9/30 (30%) and ALT is normal in 16/30 (53%) at week 24 for those receiving Pegasys + ribavirin.

Nezam Afdahl (Beth Israel Deaconness Medical Center, Boston) reported at DDW on 30 non-cirrhotic patients who did not respond previously to IFN/RBV and who received Pegasys + RBV, as part of a study in which other patients received amantadine or mycophenolate acid. The patients were treated for 48 weeks, and preliminary results were reported. The mean age of the 30 patients who received Pegasys+RBV was 45 years, the mean weight was 90 kg; 70% were male and 30% were female; the mean ALT was 113 IU/L, 60% had high HCV RNA, 90% were genotype 1, and none of the patients had cirrhosis. In this study, patients who received at least one dose of study medication and who subsequently discontinued therapy are considered nonresponders. Afdahl reported that no unexpected adverse events were seen.

The results of this study are:

--at week 24, 14/30 (46%) HCV RNA declined by at least 2 log,

--at week 12, 10/30 had negative PCR and

--at week 24 9/30 (30%) had negative PCR;

--14/30 had normal ALT at week 4, and 16/30 (53%) had normal ALT at week 24.

Preliminary data from Steven Herrine (Thomas Jefferson University Hospital; abstract 1966) was reported at DDW. In this study patients also received Pegasys/RBV or amantadine and mycophenolate acid. The patients were viral breakthroughs or relapsers. A viral breakthrough is when HCV-RNA is reduced while on therapy but rebounds while still on therapy. A relapse is when HCV-RNA is undetectable at the end of treatment but rebounds after stopping therapy. Eighty-four percent were relapsers, 78% were infected with genotype 1; 56% had a high viral, 75% were male, the average weight was 92 kg, and the average age was 48 years. At week 24, 28/32 (87%) had a reduction in HCV RNA of at least 2 log, and 22/32 (69%) had HCV RNA below assay detection (21/32 had

negative PCR by week 12). The average baseline ALT was 117 IU/L, and at week 4, 15/32 had normal ALT, and at week 24 17/32 had normal ALT.

18 months therapy for hard to treat patients: cirrhosis; high viral load, genotype 1

This study suggests that 18 months of therapy may improve the response rate for hard-to-treat populations. At the 2001 EASL Conference, an update was reported on the Benelux Study of treatment for 18 months compared to 6 months. 300 patients without previous treatment received standard IFN plus RBV 1000-1200 mg/day. Hard to treat populations received the greatest benefit: patients with genotype 1, cirrhosis, and high baseline viral load, in the as treated analysis. After 18 months treatment the SVR was 43% (ITT) compared to 34% treated (ITT) for 6 months. The relapse rate was 13% in 18 month-treatment group vs 38% in 6 month group. In the group receiving IFN alone for 18 months the SVR was 16% (ITT) and relapse rate was 39%.

Using as-treated analysis for patients who were 80% adherent for 80% of the intended duration of therapy, patients with cirrhosis receiving 18 months IFN/RBV had a **higher** SVR of 57% (as-treated analysis) compared to 42% without cirrhosis. For patients receiving 6 months treatment the opposite occurred, as expected: those with cirrhosis had SVR of 29% compared to 37% without cirrhosis (as-treated analysis).

Patients with genotype 1 receiving 18 months therapy had higher SVR than those taking 6 months treatment (36% vs 23%). But, those with genotype 2 or 3 had the same SVR (71-72%) regardless of the duration of therapy.

Patients with high HCV RNA at baseline (> 3 million copies/ml) and 18 months of treament had better SVR than those who received 18 months of treatment with HCV RNA < 3 million copies/ml (42% vs 18%). Individuals with HCV RNA < 3 million copies/ml had the same SVR (47%-49%) whether they received 18 or 6 months of therapy (as-treated analysis).

Conclusions

The optimal time to initiate treatment of HCV in HIV/HCV coinfected individuals is very important and will require additional investigation. It is clear that the immune response against HCV is an important determinant of who is likely to respond to antiviral treatment and who is not. How the HCV-specific immune response is compromised in the setting of HIV has not been determined.

Even with the advent of new therapies to treat HCV, including pegylated interferon in combination with ribavirin, many HCV-infected individuals will fail to respond. Therefore future investigation will be required to determine the optimal time to initiate treatment of HCV and to develop new therapeutic modalities that can be used to treat HCV in both HCV monoinfected and HIV/HCV coinfected individuals.